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ORIGINAL ARTICLE


# Efficacy and safety of bulevirtide in patients with chronic hepatitis D treated under early access in Switzerland: a retrospective analysis

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## Summary

BACKGROUND AND AIMS: Bulevirtide 2 mg/day was approved in Switzerland in February 2025 for the treatment of chronic hepatitis D virus (HDV) infection. We present real-world data on efficacy and safety in patients treated under an early access programme.

METHODS: This retrospective, multicentre Swiss cohort study included patients with compensated HDV-associated cirrhosis in whom bulevirtide therapy (2 mg/day) was initiated between January 2020 and August 2024 under a compassionate use programme. Virological response was defined as a HDV RNA level that was undetectable or declined ≥2 $\log_{10}$ IU/ml from baseline. Biochemical response was defined as normalisation of ALT. Combined response was defined as achieving both virological and biochemical response. Liver-related events and adverse events were assessed.

RESULTS: Fourteen patients with compensated HDV-related cirrhosis received bulevirtide for a median duration of 1.85 years (1.1–2.1). Median age was 51.3 years (43.9–58.5), and 71.4% were men. Baseline ALT was 81 U/l (55.8–88.8), platelet count 102.5 × $10^9$/l (67.3–141.3) and liver stiffness 15.3 kPa (11.8–22.1). Baseline HDV RNA was 4.82 $\log_{10}$ IU/ml (4.52–6.23). Biochemical, virological and combined responses were observed in 50%, 64.3% and 35.7% at 6 months; 66.7%, 75% and 58.3% at 12 months; and 62.5% for all three response types at 24 months. Two patients (14.3%) developed de novo hepatocellular carcinoma, and one (7.14%) patient underwent liver transplantation. No serious adverse events were reported. Mild transient pruritus occurred in two (14.3%) patients.

CONCLUSIONS: In this real-world cohort of patients with compensated HDV cirrhosis, bulevirtide demonstrated favourable efficacy and safety. These findings support the integration of bulevirtide into routine care for patients with HDV and compensated cirrhosis in Switzerland following its reimbursement status as of 2025. Longer-term follow-up is warranted to assess the impact on liver-related outcomes.

**ABBREVIATIONS**
**ALT** alanine aminotransferase
**ANA** anti-nuclear antibodies
**EMA** European Medicines Agency
**HBV** hepatitis B virus
**HCV** hepatitis C virus
**HDV** hepatitis D virus
**HIV** human immunodeficiency virus
**IFN** interferon
**INR** international normalised ratio

## Introduction

Hepatitis D virus (HDV) is a single-stranded ribonucleic acid (RNA) defective virus that requires the hepatitis B surface antigen (HBsAg) to enter hepatocytes, complete its life cycle and cause liver damage [1]. It is estimated to affect approximately 12–20 million people worldwide, corresponding to 4.5–13% of all HBsAg-positive carriers [2, 3]. Acute infection can cause acute liver failure, while persistent infection typically causes the most severe form of chronic viral hepatitis, which is associated with rapid and frequent progression to cirrhosis and its end-stage complications, hepatic decompensation and hepatocellular carcinoma [1]. Until recently, no effective antiviral therapy was available. In past decades, interferon-α (IFN-α)-based treatment has been used to treat HDV, which was effective in only 25–30% of patients [4]. Apart from low efficacy rates, IFN-α-associated side effects and contraindications resulted in limited IFN-α treatment applicability, especially in advanced liver disease [1]. More recently, the HDV entry inhibitor bulevirtide, a linear 47-amino-acid chemically synthesised lipopeptide that specifically binds to the HBV/HDV entry receptor Na+-taurocholate-co-transporting polypeptide (NTCP), was developed, thus preventing hepatocyte infection. In July 2020, bulevirtide 2 mg received conditional marketing authorisation by the European Medicines Agency (EMA) for the treatment of chronic hepatitis D virus infection (CHD), after positive results regarding safety and efficacy in phase II and III trials [5–8]. Recently published data on real-world effectiveness and safety of bulevirtide monotherapy for up to 96 weeks in patients with HDV-related cirrhosis, from the SAVE-D study, confirmed the positive results from the registration trials [9].

In Switzerland, bulevirtide was accessible through a compassionate use programme before official approval in February 2025. This study presents real-world data from Switzerland on the efficacy and safety of bulevirtide in patients with compensated HDV-associated cirrhosis included in this programme.

## Patients and methods

This was a multicentre retrospective cohort study conducted in five centres across Switzerland. Consecutive patients with compensated HDV-related cirrhosis starting bulevirtide 2 mg/day between January 2020 and August 2024 with a follow-up of at least six months were included. Follow-up was calculated from baseline to the date of liver-related event, death or last follow-up. Chronic hepatitis D infection was defined as HDV RNA positivity for at least 6 months. Data was collected at the start of treatment, after six months and yearly thereafter. The compassionate use programme was only available for patients with compensated liver cirrhosis. Diagnosis of cirrhosis was based on liver biopsy, non-invasive tests such as liver stiffness measurement (LSM) >12.5 kPa [1, 10], imaging findings (nodular liver, splenomegaly) or laboratory parameters (thrombocytopenia). All patients had detectable HDV RNA and HBsAg positivity. The primary outcome was the rate of virological and/or biochemical response. Virological response was defined as an HDV RNA level that was undetectable or declined ≥2 log10 IU/ml from baseline. Biochemical response was defined as normalisation of alanine aminotransferase (ALT). Secondary outcomes were the occurrence of side effects, liver-related outcomes and assessment of change in liver stiffness measurement during the observation period. Data on clinical (including adverse events), biochemical, virological and imaging parameters were retrospectively collected from electronic patient records. The present manuscript was drafted in accordance with STROBE cohort study reporting guidelines.

### Treatment regimen

Bulevirtide was administered at a dose of 2 mg/day subcutaneously. In some cases, bulevirtide was combined with pegylated interferon-α, based on physician discretion and patient-specific factors. Additionally, all patients were receiving a nucleos(t)ide analogue as part of standard therapy for chronic hepatitis B. The first patient was initiated on bulevirtide in January 2020. Subsequently, additional patients were enrolled and treated under the compassionate use programme. This programme remained active until 31 January 2025. As of 1 February 2025, bulevirtide has become reimbursable through the Swiss health insurance system and is now available as part of standard clinical care. All patients continued therapy under this reimbursement framework. Duration of bulevirtide therapy and any treatment modifications were documented. Adherence was monitored through regular clinical follow-up.

### Statistical analysis

Categorical variables are expressed as counts and percentages; continuous variables are expressed as medians and interquartile ranges (IQR, $25^{th}$–$75^{th}$ percentile). Fisher's exact test was used to compare categorical data between two groups. The Wilcoxon rank-sum test was used to compare quantitative data between two groups. p-values <0.05 (two-tailed) were considered significant in all analyses. Statistical analysis was performed using R version 4.2.

### Ethical approval

The study was approved by the Cantonal Ethics Committee of Bern, Switzerland (2024-01399). Written informed consent was given by all patients.

## Results

### Study population and baseline characteristics

A total of 14 patients were enrolled with a median follow-up of 1.85 years (1.1–2.1). Patients were recruited from Bern (n = 8, 57%), St Gallen (n = 2, 14%), Zurich (n = 2, 14%), Fribourg (n = 1, 7%) and a private practice in Zurich (n = 1, 7%). Baseline demographic, virological and clinical characteristics are summarised in table 1. The presumed route of HDV transmission was intravenous drug use in 5 patients (36%), perinatal in 1 (7%) and unknown in 7 (50%). One additional patient (7%) had either a history of drug use or transfusion. All patients with a history of intravenous drug use were of Swiss origin. Half of the patients were of Swiss origin (n = 7, 50%), with others originating from Mongolia (n = 3, 21%), Turkey (n = 2, 14%) and Africa (n = 2, 14%).

All patients had compensated liver cirrhosis (Child-Pugh A) at baseline. Five patients (36%) had endoscopically confirmed oesophageal varices; two (14%) received non-selective beta-blockers, one (7%) underwent ligation and one (7%) had beta-blocker intolerance. One patient (7%) had a history of treated hepatocellular carcinoma prior to bulevirtide initiation. Comorbidities included arterial hypertension (n = 3), diabetes mellitus (n = 1), chronic kidney disease (n = 1), chronic pancreatitis (n = 1), coronary heart disease (n = 1) and previous cancer (n = 2; cervical cancer and non-invasive bladder cancer).

Two patients (14%) reported current low-level alcohol intake (≤5 g/week), while three (21%) had a history of past alcohol use. Four patients (29%) reported active nicotine use. No patient reported ongoing illicit drug use at the time of treatment initiation.

**Table 1:** Patient baseline characteristics at treatment start with bulevirtide. Categorical variables are presented as n (%). Continuous data are presented as median and interquartile range (IQR, 25th–75th percentile).

| Baseline variable | | Overall (n = 14) | Missing data, n (%) |
|---|---|---|---|
| Demographics | Age at treatment start, years | 51.3 (43.9–58.5) | 0 (0%) |
| | Age at diagnosis of HBV, years | 33.3 (31.7–40.1) | 1 (7%) |
| | Age at diagnosis of HDV, years | 37.1 (33–45) | 1 (7%) |
| | Male sex, n (%) | 10 (71%) | 0 (0%) |
| | Caucasian, n (%) | 7 (50%) | 0 (0%) |
| | Treated HCV coinfection, n (%) | 4 (29%) | 0 (0%) |
| | Treated HIV coinfection, n (%) | 1 (7%) | 0 (0%) |
| | MASLD, n (%) | 2 (14%) | 0 (0%) |
| | Body mass index, kg/m$^2$ | 23.6 (21.8–26.5) | 0 (0%) |
| Biochemistry | ALT, × ULN | 1.65 (1.5–1.98) | 0 (0%) |
| | AST, × ULN | 1.5 (1.1–1.73) | 0 (0%) |
| | Alkaline phosphatase, × ULN | 0.8 (0.7–0.95) | 1 (7%) |
| | Bilirubin total, µmol/l (REF: <17 µmol/l) | 8.9 (7.25–12.5) | 0 (0%) |
| | Albumin, g/l (REF: 35–52 g/l) | 34.5 (33.15–38.2) | 0 (0%) |
| | INR (REF: <1.2) | 1.1 (1.02–1.2) | 0 (0%) |
| | Creatinine, µmol/l (REF: 59–104 µmol/l) | 75 (66–82) | 1 (7%) |
| | Platelets, 10$^9$/l (REF: 150–450 10$^9$/l) | 102.5 (67.3–141.3) | 0 (0%) |
| | Bile acids, µmol/l (REF: 0–10 µmol/l) | 10.8 (9.9–13.2) | 7 (50%) |
| Virology | HBsAg, IU/ml | 7469 (2373–14,287) | 2 (14%) |
| | HBsAg-positive, n (%) | 1 (7%) | 4 (29%) |
| | HBV DNA detectable, n (%) | 9 (64%) | 0 (0%) |
| | HBV DNA, IU/ml | 16 (14–23) | 0 (0%) |
| | HDV RNA, IU/ml | 66,718 (33,250–1,714,924) | 0 (0%) |
| | HDV RNA, $\log_{10}$ IU/ml | 4.82 (4.52–6.23) | 0 (0%) |
| Assessment of liver disease | Child A, n (%) | 14 (100%) | 0 (0%) |
| | MELD score | 8 (7–8) | 0 (0%) |
| | METAVIR F3–F4, n (%) | 9 (69%) | 1 (7%) |
| | Liver stiffness measurement, kPa | 15.3 (11.8–22.1) | 1 (7%) |
| | Cirrhotic aspect on imaging, n (%) | 8 (57%) | 0 (0%) |
| | Spleen diameter, cm | 11.2 (10–14) | 1 (7%) |
| | Oesophageal varices, n (%) | 5 (36%) | 5 (36%) |
| Clinical events | History of hepatocellular carcinoma, n (%) | 1 (7%) | 0 (0%) |
| Treatment | Previous IFN treatment, n (%) | 8 (57%) | 0 (0%) |
| | Concurrent IFN treatment*, n (%) | 1 (7%) | 0 (0%) |
| | NUC treatment for HBV, n (%) | 14 (100%) | 0 (0%) |
| | Duration of NUC treatment before bulevirtide start, years | 3.24 (0.44–5.05) | 1 (7%) |

* Two patients had previous IFN treatment and were again started at a later time point.
ALT: alanine aminotransferase; ANA: anti-nuclear-antibodies; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; IFN: interferon; INR: international normalised ratio; MASLD: metabolic dysfunction-associated steatotic liver disease; MELD: model of end-stage liver disease; NUC: nucleos(t)ide analogue; REF: reference range; ULN: upper limit of normal.

### Virological and biochemical response

Treatment with bulevirtide resulted in a significant reduction in HDV RNA levels over time. Median HDV RNA declined from 4.82 (4.52–6.2) $\log_{10}$ IU/ml at baseline to 3.45 at month 6 (2.0–4.14, p <0.001), 2.63 at month 12 (2.0–3.57, p <0.001) and 2.28 at month 24 (2.0–3.48, p = 0.016). Individual responses are shown in figure 1. In parallel, median ALT levels decreased from 81 U/l (55.8–88.8) at baseline to 46 U/l (33–58.3) at 6 months (p = 0.006), and remained within the normal range thereafter. Biochemical and virological response rates over time are summarised in figure 2.

**Figure 1:** HDV RNA levels during bulevirtide 2 mg/day therapy up to 60 months. The apparent decline in patient numbers over the 60-month observation period does not reflect treatment discontinuation or loss to follow-up. Rather, it results from staggered treatment initiation across the cohort, with only two patients having initiated therapy as early as 2020. All patients – except one with former intravenous drug use and the transplanted patient – remained on treatment and under observation until the end of the study period. This temporal context should be considered when interpreting longitudinal response data. The blue area indicates that the viral load is below the test's lower limit of quantification. HDV RNA: hepatitis D RNA.

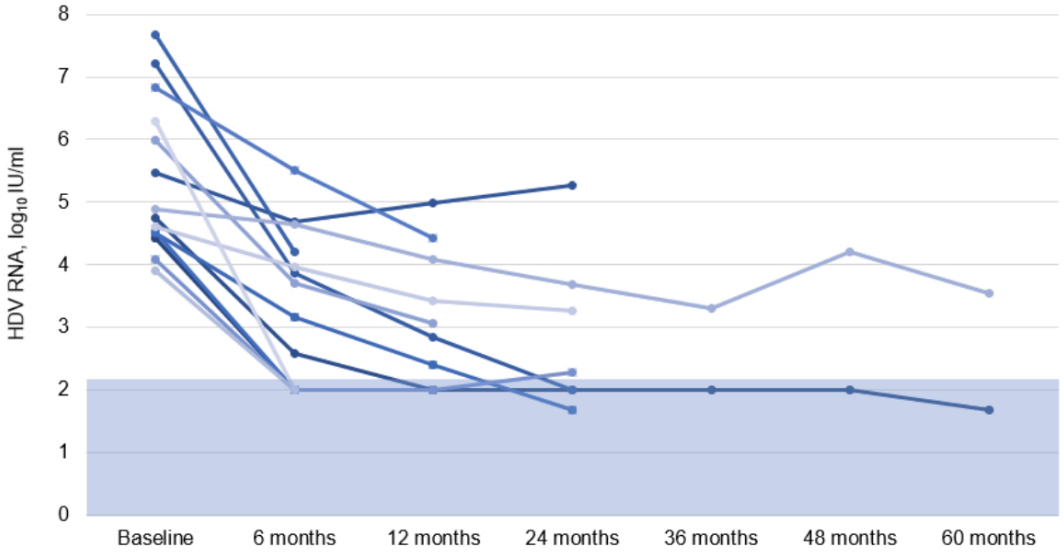
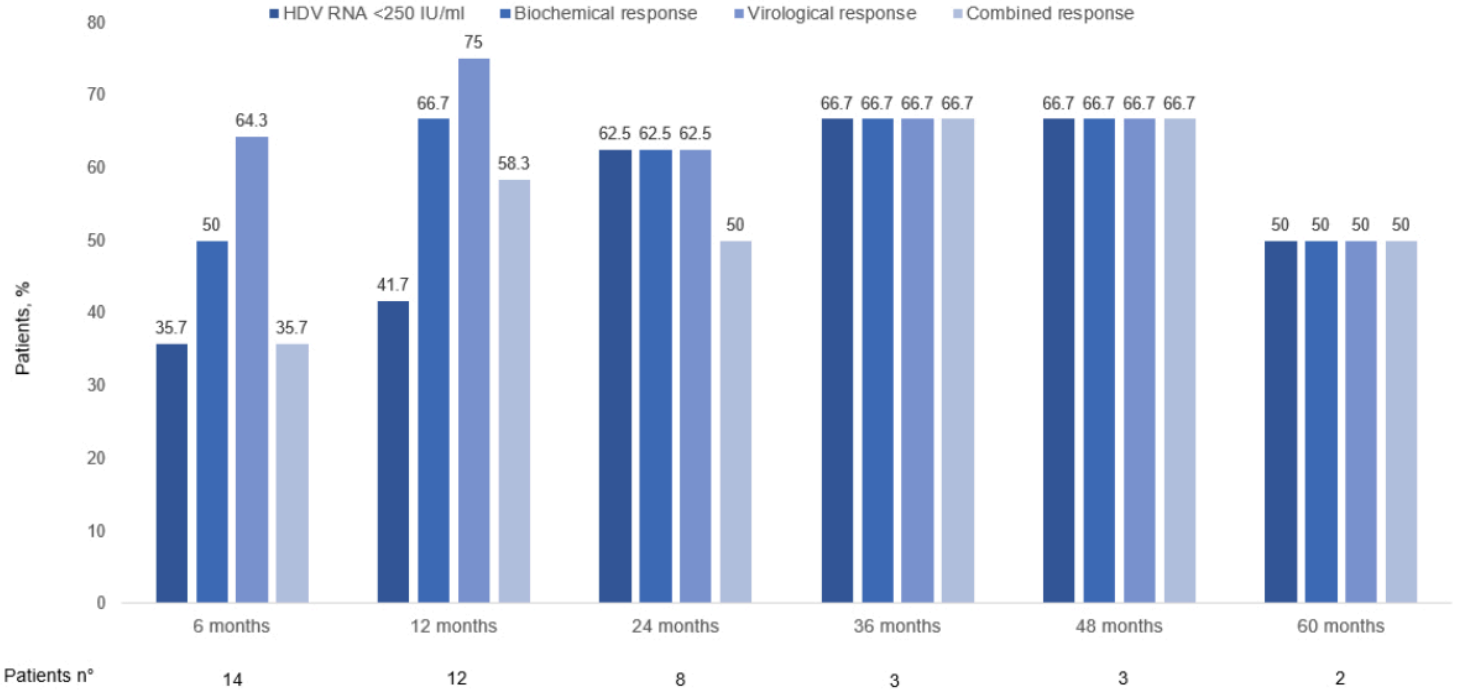


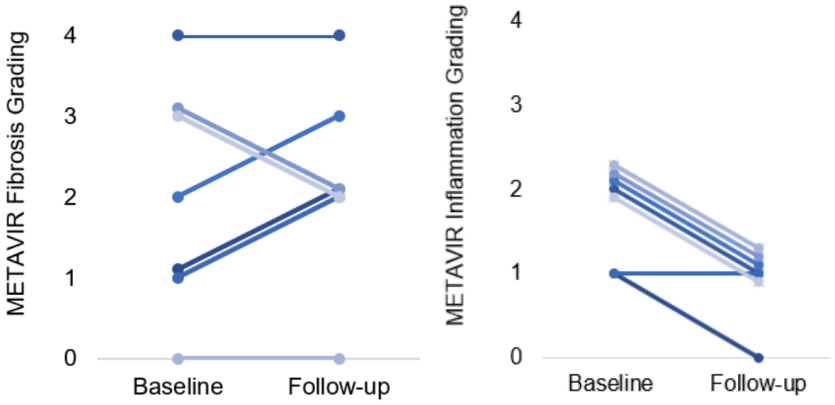

**Figure 2:** Rates of biochemical, virological and combined responses to bulevirtide treatment for up to 60 months.The apparent decline in patient numbers over the 60-month observation period does not reflect treatment discontinuation or loss to follow-up. Rather, it results from staggered treatment initiation across the cohort, with only two patients having initiated therapy as early as 2020. All patients – except one with former intravenous drug use and the transplanted patient – remained on treatment and under observation until the end of the study period. This temporal context should be considered when interpreting longitudinal response data.



### Histological changes

Thirteen of the fourteen patients (93%) underwent a liver biopsy prior to treatment initiation, with a median interval of 2.88 years (0.73–2.98) between biopsy and bulevirtide initiation. At baseline, 5 patients (38%) were staged as F4, 4 (31%) as F3, 1 (8%) as F2, 2 (15%) as F1 and 1 (8%) as F0 according to METAVIR fibrosis staging. Inflammatory activity was classified as A2 in 8 patients (73%) and A1 in 3 patients (27%), with data missing in 2 cases. During follow-up, 7 patients underwent a repeat liver biopsy at a median of 1.16 years (1.06–1.90) after treatment initiation. Figure 3 illustrates the individual changes in METAVIR fibrosis stages and inflammatory activity grades in these patients.

**Figure 3:** METAVIR grading of fibrosis and inflammation on liver histology before bulevirtide treatment and during follow-up. Only patients with a biopsy before and during treatment are represented on this graph (n = 7).




### Liver stiffness measurement

Baseline liver stiffness measurements (LSM) were available in 13 of 14 patients (93%), with a median value of 15.3 kPa (11.8–18.94). The median time between baseline LSM and treatment initiation was 0.67 years (0.28–1.23). During follow-up, LSM was repeated in 8 patients (57%). In this subgroup, median LSM decreased from 14.05 kPa (11.3–17.0) at baseline to 9.15 kPa (5.5–13.7) at follow up ($p = 0.161$). The median interval between treatment initiation and the most recent LSM was 1.93 years (1.36–2.48).

### Liver-related events and survival

*Decompensation, hepatocellular carcinoma and liver transplantation*

One patient (7%) developed ascites at month 36, which persisted until the end of follow-up. No additional events of hepatic decompensation were reported. Another patient (7%) developed a portal vein thrombosis after 48 months of treatment, in the absence of hepatocellular carcinoma. Two patients (14%) were diagnosed with hepatocellular carcinoma during follow-up: one at month 6 and one at month 12. Both were treated with local therapy. One of these patients had a known history of hepatocellular carcinoma prior to bulevirtide initiation and developed recurrent lesions during treatment. This patient ultimately underwent liver transplantation 13 months after starting bulevirtide.

*Adverse events and treatment compliance*

Bile acid levels increased from a median of 10.8 µmol/l at baseline (9.9–13.2, n = 7) to 55.8 µmol/l (23.2–96.2) at last follow-up. Two patients (14%) reported mild pruritus at month 6, which resolved spontaneously. No further adverse events were reported during treatment. One patient (7.14%) discontinued therapy due to non-compliance. This patient had a history of substance use and psychosocial instability, which likely contributed to treatment discontinuation.

## Discussion

This study presents long-term real-world data on the efficacy and safety of bulevirtide 2 mg/day in patients with HDV infection and compensated liver cirrhosis treated within a compassionate use programme in Switzerland, with a follow-up of up to 60 months.

The baseline characteristics of our cohort were comparable to those reported in the registration study [8] and the SAVE-D study [9], with similar levels of disease severity, prior interferon exposure, and biochemical and virological parameters. Our cohort had a higher proportion of non-Caucasian patients and men, and three patients received concomitant pegylated interferon-α therapy, which was not used in the SAVE-D study [9].

Biochemical response rates, defined by ALT normalisation, were comparable to published data (66.7% in our cohort vs 60–64% in previous studies) [8, 9]. The decline in response rate at month 60 (50%) is difficult to interpret due to the low number of patients (n = 2) at that time point.

Virological response rates in our study (66.7–75% up to month 48) were also in line with previously reported data (76–79%) [8, 9]. Combined response rates were similar to those in the SAVE-D trial [9].

One patient discontinued treatment due to non-adherence. This individual had a history of intravenous drug use, benzodiazepine and opioid dependency, and psychosocial instability, highlighting the need for personalised adherence strategies in vulnerable populations.

Importantly, all patients were included based on a clinical diagnosis of compensated cirrhosis, established using non-invasive tests such as liver stiffness measurement (LSM), typical imaging and laboratory findings. Histological confirmation was not required, and in some cases liver biopsies revealed fibrosis stages inconsistent with cirrhosis. This likely reflects sampling variability and the recognised limitations of liver biopsy in staging HDV-related liver diseases, particularly in heterogeneous or patchy fibrosis. All patients in our cohort were already receiving nucleos(t)ide analogue therapy for HBV prior to initiation of bulevirtide. Therefore, it is also conceivable that some patients experienced partial regression of fibrosis under long-term HBV suppression, contributing to the discrepancy between clinical staging and histological findings. Interestingly, in three patients, the follow-up biopsy showed a higher fibrosis stage compared to baseline histology, as illustrated in figure 3. This observation appears paradoxical in the context of concurrent virological and biochemical improvement. Several factors may contribute to this finding. First, liver biopsy is subject to sampling variability, especially in diseases such as HDV where fibrosis is heterogeneously distributed [11, 12]. It is possible that fibrosis was underestimated in the initial biopsy and better captured in the follow-up specimen. Second, semi-quantitative scoring systems such as METAVIR are susceptible to interobserver variability, particularly in distinguishing between advanced stages [13]. These considerations underline the interpretive limitations of liver histology in HDV and reinforce the value of combining biopsy with longitudinal non-invasive assessments for reliable staging and monitoring.

Our findings underscore the relevance of integrating non-invasive tests into clinical decision-making for patient selection and monitoring in HDV, as also recommended by EASL guidelines [1]. Follow-up histology in seven patients demonstrated reduced inflammatory activity in most cases, consistent with biochemical and virological improvement.

In parallel, LSM decreased from a median of 14.05 to 9.15 kPa during follow-up in a subgroup of eight patients. Although this reduction did not reach statistical significance ($p = 0.161$), it mirrors the improvements seen in laboratory and histological parameters, and suggests a trend towards fibrosis regression with ongoing therapy.

Notably, two patients (14%) developed de novo hepatocellular carcinoma, and one underwent liver transplantation. These rates are higher than in the SAVE-D study (hepatocellular carcinoma 2.5%) [9], likely reflecting the advanced disease stages of patients included in the compassionate use programme, where enrolment was limited to high-risk individuals. One additional patient experienced hepatic decompensation. These findings highlight the aggressive nature of HDV and the importance of early antiviral intervention.

Safety and tolerability of bulevirtide were excellent. Only two patients reported mild, transient pruritus, and no serious adverse events were observed. Despite the requirement for daily subcutaneous administration, adherence was high in all but one patient. Bile acid levels increased during therapy, as expected with NTCP inhibition, but without clinical consequences.

Limitations of this study include the small cohort size, its retrospective design and heterogeneous HDV RNA assays across participating centres. These factors limit direct comparison of absolute viral load changes. Nonetheless, the consistent trends in virological and biochemical response support the overall validity of our findings. The main strength of this study is its real-world nature and the inclusion of long-term follow-up data from multiple Swiss centres, providing valuable insight into national treatment experience.

### Conclusions

This real-world Swiss cohort confirms the antiviral efficacy and favourable safety profile of bulevirtide in patients with compensated HDV-related cirrhosis, including those with features of portal hypertension. Bulevirtide was well tolerated and associated with sustained virological and biochemical responses. Future studies with larger sample sizes and longer follow-up are needed to evaluate the long-term impact of bulevirtide on liver-related outcomes and disease progression.

## Data sharing statement

The data supporting the findings of this study is not publicly available due to ethical restrictions. However, aggregated or summarised data may be available from the corresponding author upon reasonable request.

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**Author contributions:** MK: initiation, data acquisition, analysis, writing the draft, finalising the manuscript; NS: conceptualisation, writing the draft, revision and approval of the final manuscript; all other authors: data acquisition, revision and approval of the final manuscript.

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### Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. The early access programme was carried out by Gilead. BH is supported by Gilead. DS and NS are members of a Gilead advisory board.

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