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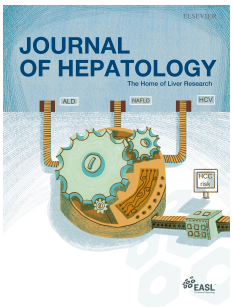

144 Weeks of bulevirtide monotherapy for chronic hepatitis D: Final and posttreatment results from a Phase 3 randomized trial

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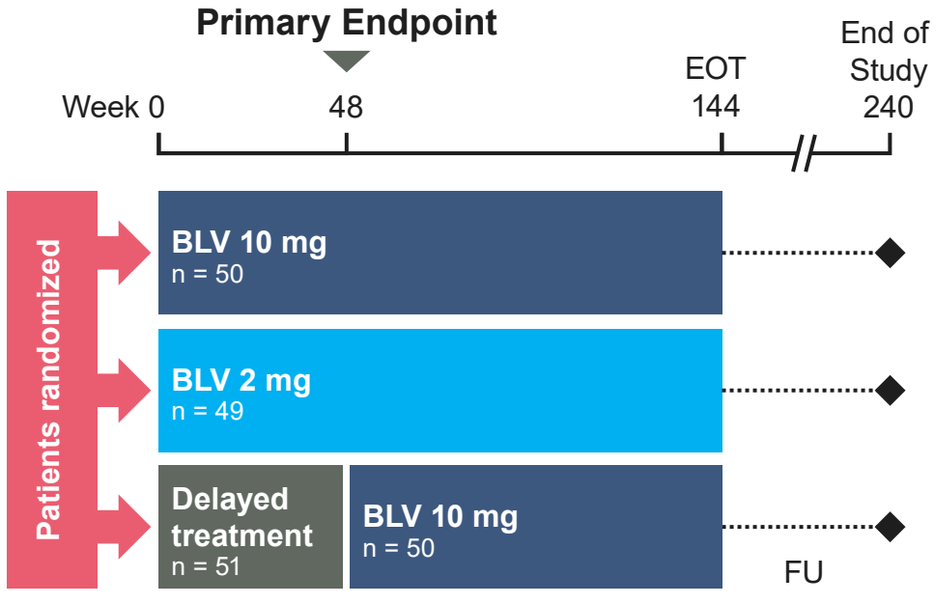
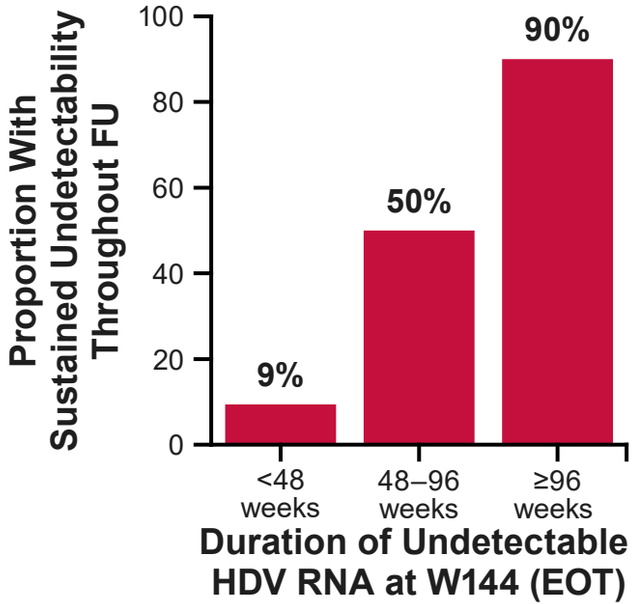
Bulevirtide for Chronic Hepatitis D: Final Results of MYR301

Design



Results

	ALT Normalization		Virologic Response*		HDV RNA Undetectability	
	W144 (EOT)	W240 (FU96)	W144 (EOT)	W240 (FU96)	W144 (EOT)	W240 (FU96)
BLV 10 mg	60%	32%	76%	30%	50%	22%
BLV 2 mg	59%	24%	73%	33%	29%	20%
Delayed treatment → BLV 10 mg	58%	28%	92%	32%	52%	20%



Conclusion

Bulevirtide is safe and effective through 3 years of treatment. Response rates decreased after EOT, but some patients had sustained undetectable HDV RNA, as predicted by a longer duration of continuous HDV RNA undetectability at EOT.

*Virologic response was defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL HDV RNA decline from baseline.
ALT, alanine aminotransferase; BLV, bulevirtide; EOT, end of treatment; FU, follow-up; FU96, follow-up at 96 weeks after EOT; W, week.

Title: 144 Weeks of bulevirtide monotherapy for chronic hepatitis D: Final and posttreatment results from a Phase 3 randomized trial☆

Short title: Bulevirtide for CHD: Final results of MYR301

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Conflict of interest statement

HW reports grant funding from Biotest; Gilead Sciences, Inc.; and Madrigal Pharmaceuticals; and honoraria for lectures, speakers bureaus, or consulting from Abbott Laboratories; Abbott Molecular; Alfasigma; Aligos Therapeutics; AstraZeneca; Atea Pharmaceuticals; BioMarin Pharmaceutical; Biotest; Bluejay Therapeutics; Bristol Myers Squibb; CSL Behring; Dr. Falk Pharma; Falk Foundation; Gilead Sciences, Inc.; GSK; IntegerBio; Ipsen; Lilly Deutschland; Madrigal Pharmaceuticals; Merck Sharp & Dohme; Mirum Pharma Germany; Orphalan; Pfizer; Primmune Therapeutics; Ribocure Pharmaceuticals; Roche; Sanofi–Aventis Deutschland GmbH; Takeda Pharma Vertrieb; and Vir Biotechnology**. SAleman** received a grant and speaking fees from Gilead Sciences, Inc., and participated on a data safety monitoring board or advisory board for Gilead Sciences, Inc., and Ribocure. **ABlank** received research funding from MYR GmbH. **PA** has received honoraria for lectures from Gilead Sciences, Inc., and Intercept

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Data availability statement: Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datasharing@gilead.com.

Clinical trial number: NCT03852719

Abstract

Background & Aims

Bulevirtide 2 mg/day is approved in Europe, Australia, Russia, and Canada for treatment of compensated chronic hepatitis D (CHD). However, long-term outcomes after treatment discontinuation are unknown.

Methods

Patients with CHD (n=150) were randomized to immediate treatment with bulevirtide 2 mg/day (n=49) or 10 mg/day (n=50) for 144 weeks (W), or 48W of delayed treatment (DT; n=51) followed by bulevirtide 10 mg/day for 96W (DT/10 mg; n=50), and 96W of posttreatment follow-up (FU96) in the MYR301 study. Efficacy endpoints included virologic response (VR; undetectable hepatitis D virus [HDV] RNA or ≥2 $\log_{10}$ IU/mL decline from baseline), combined response (CR; VR and alanine aminotransferase [ALT] normalization), ALT normalization, and undetectable HDV RNA.

Results

At the end of treatment (EOT), response rates in the 2, 10, and DT/10 mg groups were: VR, 73%, 76%, and 92%; ALT normalization, 59%, 60%, and 58%; CR, 57%, 54%, and 56%; HDV RNA undetectability, 29%, 50%, and 52%. At FU96, VR rates declined to 33%, 30%, and 32%, respectively; CR rates were 24% across all groups. HDV RNA undetectability rates were 20%, 22%, and 20% at FU96. Sustained undetectability through follow-up was observed in 23/64 (36%) patients with undetectable HDV RNA at EOT, with weeks continuously undetectable at EOT being the most important predictor

of sustained undetectability. Posttreatment hepatic serious adverse events occurred in 20/142 (14%) patients and resolved in 17/20 (85%).

Conclusions

Bulevirtide treatment for CHD for up to 144W was safe and effective. Response rates decreased after treatment discontinuation; however, some patients had sustained undetectable HDV RNA throughout 2 years of follow-up. (Funded by Gilead Sciences; MYR301 ClinicalTrials.gov number, NCT03852719).

Impact and implications

Although bulevirtide is approved for treatment of chronic hepatitis D (CHD) in the European Economic Area, the United Kingdom, Switzerland, the Russian Federation, Australia, and Canada, treatment outcomes beyond 2 years and after bulevirtide discontinuation remain unknown. In this analysis, we demonstrate that efficacy was maintained with bulevirtide monotherapy for up to 144 weeks compared with that at 96 weeks, while rates of HDV RNA undetectability continued to improve with extended treatment duration. Virologic and biochemical responses decreased after treatment discontinuation, but some patients who were undetectable at EOT maintained HDV RNA undetectability posttreatment, with duration of continuous HDV RNA undetectability at EOT being the strongest predictor of non-relapse. While most patients benefit from continued bulevirtide therapy, a subset of those who achieve undetectable HDV RNA may be able to discontinue treatment without loss of response even in the absence of HBsAg loss.

Introduction

HDV infection causes the most severe form of chronic viral hepatitis, affecting approximately 9 to 19 million people globally.[1] HDV is a defective RNA virus that requires the HBsAg as its envelope protein for propagation.[2,3] Chronic hepatitis D (CHD) leads to a more rapid progression to cirrhosis,[4] resulting in up to a 3-fold increased risk of hepatocellular carcinoma compared with HBV monoinfection.[5] It is associated with a mortality rate exceeding 35% over a 10-year period.[6]

Bulevirtide, a first-in-class entry inhibitor, is a 47–amino-acid lipopeptide that binds to the sodium taurocholate cotransporting polypeptide (NTCP) and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes.[7] Interim data from the Phase 3 study MYR301 demonstrated that bulevirtide 2 or 10 mg monotherapy was well tolerated and efficacious through week (W) 48 when compared with control.[8] Virologic and biochemical response rates further improved with longer treatment duration in a W96 interim analysis.[9] Patients with suboptimal virologic responses to bulevirtide at W24 also benefitted from continued therapy; most achieved virologic response and biochemical improvement by W96.

Following approval of bulevirtide in the European Economic Area, other European countries, Australia, the Russian Federation, and Canada, the European Association for the Study of the Liver now recommends bulevirtide 2 mg/day subcutaneously (s.c.) for treatment of CHD.[10-13] No therapies for CHD are approved in the United States. Real-world data from bulevirtide-treated patients in Europe support its safety and efficacy and provide the first evidence for reduced rates of liver-related outcomes, including hepatic decompensation.[14-17] Long-term outcomes after treatment

discontinuation remain unknown. We present final results of MYR301, including efficacy and safety of bulevirtide monotherapy in patients with CHD through up to 144 weeks of treatment and 96 weeks of posttreatment follow-up. We also describe the durability and predictors of sustained virologic undetectability after bulevirtide discontinuation.

Methods

Study design

The methodology and protocol for MYR301 have been previously published.[8,9] MYR301 was an open-label, parallel-group, multicenter Phase 3 study (ClinicalTrials.gov identifier: NCT03852719). Eligible patients were randomized in a 1:1:1 ratio and stratified by presence or absence of cirrhosis. Patients were randomized into three groups: immediate treatment with bulevirtide 2 mg/day s.c. or 10 mg/day s.c. for 144 weeks, or delayed treatment (DT), where no study treatment was administered during the first 48 weeks, followed by bulevirtide 10 mg/day s.c. for 96 weeks. At the end of treatment (EOT), all patients entered a 96-week off-therapy follow-up period (FU96; **Fig. S1**).

Trial oversight

HW, DM, and PL contributed to the conception and design of the trial. All authors contributed to data collection, interpretation, and drafting of the original manuscript. Gilead Sciences, Inc., the trial sponsor, conducted the data analysis and provided writing assistance. All authors approved the final manuscript and affirm the trial's

adherence to the protocol (available at sciencedirect.com), the accuracy and completeness of the data, and the integrity of the analysis.

All patients provided written informed consent. The protocol was approved by the review board or ethics committee at each trial site prior to initiation. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declarations of Helsinki and Istanbul.

Patients

Inclusion and exclusion criteria have been previously published and are available in the **Supplementary Methods**.[8,9] Key inclusion criteria were CHD with or without cirrhosis, alanine aminotransferase (ALT) levels >1 to <10 × the upper limit of normal (ULN), HDV RNA detected by PCR at screening, and compensated liver disease with a Child-Turcotte-Pugh score of ≤7 points. Concomitant HBV treatment with nucleos(t)ide analogues (NAs) was allowed.

Assessments

Assessments have been previously published and are detailed further in the **Supplementary Methods**.[8,9] HDV RNA levels were quantified using the RoboGene HDV RNA Quantification Kit, version 2.0 (Roboscreen), with a lower limit of quantitation (LLOQ) of 50 IU/mL and a lower limit of detection of 6 IU/mL. Undetectable HDV RNA was defined as an HDV RNA value <LLOQ with target not detected. HDV RNA relapse was defined as HDV RNA undetectable at EOT and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA. HDV rebound was defined as an

increase in HDV RNA of ≥2 $\log_{10}$ IU/mL from the LLOQ of 50 IU/mL (if HDV RNA <LLOQ at EOT) or an increase of ≥2 $\log_{10}$ IU/mL posttreatment compared with EOT. HBV reactivation was defined as any of the following during the posttreatment period: any HBV reactivation adverse event (AE) term; a change from negative HBsAg status (at EOT or during the posttreatment period) to positive HBsAg status; or an increase in HBV DNA ≥3 $\log_{10}$ IU/mL if HBV DNA was undetectable at EOT, or an increase of ≥2 $\log_{10}$ IU/mL if not.

Endpoints

The primary endpoint of the trial, which was previously reported,[8,9] was a combined response of ALT normalization and virologic response (undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL HDV RNA decline from baseline) at W48. We present an intention-to-treat (ITT), missing-equals-failure (MEF) analysis for the following prespecified and exploratory efficacy endpoints at EOT (W144) and through FU96: ALT normalization, virologic response, combined response, undetectable HDV RNA, change in liver stiffness, and HBsAg response (HBsAg decrease by ≥1 $\log_{10}$ IU/mL from baseline) and loss. Additionally, liver-related outcomes and AEs are summarized.

Exploratory analyses

<u>Predictors of sustained posttreatment undetectable HDV viremia</u>

While this study was designed to evaluate longer-term treatment with bulevirtide for up to 144 weeks through the primary endpoint of combined response, we performed a post hoc analysis to identify predictive factors associated with sustained viral

suppression after stopping treatment. Patients with undetectable HDV RNA at EOT and available follow-up data for at least one posttreatment visit were included. Sustained posttreatment undetectability was defined as undetectable HDV RNA at all available follow-up visits.

Subgroup analyses

Subgroup analyses evaluated combined response in patients with and without cirrhosis at baseline and in those with and without concomitant NA medications. Median total bile salt levels over time were assessed in patients stratified by presence of pruritus while on treatment; ALT levels were stratified by patients' virologic response categories at EOT, as defined in the **Supplementary Methods**.

Statistical analysis

Statistical methods have been previously published.[8] Sensitivity analyses for off-treatment follow-up visits for ALT normalization, virologic response, combined response, and HDV RNA undetectable included completers analysis for patients with nonmissing EOT and FU96 measurements (**Table S1**) and MEF analysis after exclusion of measurements collected after restart of commercial bulevirtide (**Table S2**).

Univariate logistic regression (adjusted for treatment group, with the exception of pairwise treatment group and bulevirtide dose comparisons) was performed to examine potential predictors of undetectable HDV RNA at EOT and of sustained posttreatment undetectable HDV RNA throughout follow-up. Variables considered are in the **Supplementary Methods**. Stepwise logistic regression (significance level for entry,

$P = 0.15$; significance level to stay, $P = 0.05$) was used to select a multivariate model, but only the number of weeks during which HDV RNA was continuously undetectable at EOT was selected for the final model.

Results

Patients

Baseline characteristics were previously published and were well balanced across groups (**Table 1**).[8] Most patients (92%) remained in the study at EOT, 72% completed FU48, and 57% completed FU96 (**Fig. S2; Table S3**). Withdrawal of consent (17%) was the most common reason for early discontinuation.

Efficacy

Biochemical and virologic responses

Biochemical response was similar across all treatment groups (**Fig. 1A**). ALT normalization rates at W144 were as follows: bulevirtide 2 mg, 59% (29/49); bulevirtide 10 mg, 60% (30/50); and DT/bulevirtide 10 mg, 58% (29/50); rates decreased after EOT (bulevirtide 2 mg, 27% [13/49] and 24% [12/49]; bulevirtide 10 mg, 28% [14/50] and 32% [16/50]; DT/bulevirtide 10 mg, 24% [12/50] and 28% [14/50] at FU48 and FU96, respectively). Mean ALT levels decreased with bulevirtide treatment regardless of virologic response at EOT (**Fig. S3**). Mean HDV RNA declines were more gradual than mean ALT declines (**Fig. 2**).

Virologic response rates at EOT were 73% (36/49), 76% (38/50), and 92% (46/50) in the bulevirtide 2 mg, bulevirtide 10 mg, and DT/bulevirtide 10 mg groups,

respectively, and decreased throughout follow-up (bulevirtide 2 mg, 29% [14/49] and 33% [16/49]; bulevirtide 10 mg, 40% [20/50] and 30% [15/50]; DT/bulevirtide 10 mg, 28% [14/50] and 32% [16/50] at FU48 and FU96, respectively; **Fig. 1B**).

After 24 weeks of bulevirtide therapy, 33% (49/149) patients had a suboptimal virologic response (**Fig. S4**). Overall, 50% (9/18) and 84% (26/31) of nonresponders and partial responders, respectively, became virologic responders by EOT.

Combined response

Combined response rates in the 2 mg, 10 mg, and DT/bulevirtide 10 mg groups at W144 were 57% (28/49), 54% (27/50), and 56% (28/50), respectively. Combined response rates decreased by FU48 to 22% (11/49), 20% (10/50), and 18% (9/50), respectively, and were 24% (12/49, 12/50, and 12/50) in each group at FU96 (**Fig. 1C; Table 2**). Rates were similar in patients with and without cirrhosis or concurrent NA therapy (**Fig. S5A,B**), and remained consistent when excluding posttreatment data after investigator-prescribed bulevirtide reinitiation, compared with results of the ITT MEF combined response analysis (**Table 2; Table S2**).

Undetectable HDV RNA

The proportion of patients with undetectable HDV RNA increased through EOT in all groups and was higher with bulevirtide 10 mg (bulevirtide 10 mg, 50% [25/50]; DT/bulevirtide 10 mg [after 96 weeks on bulevirtide], 52% [26/50]) than with bulevirtide 2 mg (29% [14/49]; $P = 0.040$ vs bulevirtide 10 mg group). In the univariate analysis,

baseline predictors of undetectable HDV RNA at EOT included lower baseline HDV RNA (log_{10} IU/mL) and bulevirtide 10 mg vs 2 mg (**Fig. S6**).

After stopping bulevirtide, HDV RNA undetectability declined by FU48 to 24% (12/50), 16% (8/50), and 16% (8/49) in the bulevirtide 10 mg, DT/bulevirtide 10 mg, and bulevirtide 2 mg groups, respectively, and remained similar at FU96: 22% (11/50), 20% (10/50), and 20% (10/49; **Fig. 1D; Table 2**). Most patients with undetectable HDV RNA at FU96 also had undetectable HDV RNA at EOT and FU48 (**Fig. S7A–C**); however, some showed transient positivity during follow-up (**Fig. S7D–F**). Nearly all patients with HDV RNA levels <LLOQ with target detected at EOT had increases in HDV RNA posttreatment, suggesting that achieving low-level viremia is not sufficient for sustaining viral suppression after stopping therapy (**Fig. S7A–C**).

Predictors of sustained off-treatment HDV RNA undetectability

Of 65 patients with undetectable HDV RNA at EOT, 64 had available follow-up data. Of these, 23 (36%) had sustained off-treatment undetectability. Twenty of these had available data through FU96; three discontinued the study early (FU24 or later) without relapse. Most relapses (93% [38/41]) occurred by FU24, with none between FU48 and FU96 (**Fig. 3A**). Patients with HDV RNA relapse had ALT increases from EOT and viral loads approaching baseline levels (**Fig. S8**). Patients with longer on-treatment continuous undetectability before EOT had higher rates of sustained off-treatment undetectability: 9/10 (90%) for ≥96 weeks of undetectability, 11/22 (50%) for ≥48 to <96 weeks, and 3/32 (9%) for 0 to <48 weeks (**Fig. 3B**). In univariate analysis, low baseline levels of HDV RNA and HBsAg and early and continuous on-treatment

HDV RNA undetectability at EOT predicted sustained undetectability posttreatment (**Fig. S9A**). In the multivariate analysis, the duration of continuous on-treatment HDV RNA undetectability at EOT predicted sustained undetectability posttreatment (**Fig. S9B**).

Unlike the overall study population, patients with sustained off-treatment HDV RNA undetectability maintained ALT normalization and stable median ALT from EOT to FU96 (range: 65% to 74% and 27 U/L to 32 U/L, respectively; **Table S4**).

Liver stiffness

Decreases in liver stiffness from baseline were observed in all bulevirtide treatment groups at EOT and through FU96 (**Fig. S10**). In the posttreatment period, there was a reversal of the reductions observed at EOT. From EOT to FU96, mean (SD) changes in liver stiffness from baseline were as follows: bulevirtide 2 mg, −4.9 (7.30) to −1.2 (9.34) kPa; bulevirtide 10 mg, −4.1 (5.04) to −3.1 (5.98) kPa; DT/bulevirtide 10 mg, −4.7 (7.46) to −3.2 (6.97) kPa. Patients with cirrhosis experienced larger decreases in liver stiffness from baseline than those without cirrhosis (**Fig. S11**).

HBV responses

HBsAg levels showed minimal changes from baseline both on treatment and posttreatment (**Table 2; Fig. S12**). Four patients had HBsAg loss during the study (**Fig. S13**). By EOT, one patient experienced HBsAg loss without seroconversion in the DT/bulevirtide 10 mg group, while three patients had HBsAg loss during follow-up (one in each group). In all four patients, HBsAg loss was sustained through FU96 and

associated with undetectable HDV RNA; no instance was associated with ALT flares >5 × ULN. HBsAg response was also uncommon, occurring in three patients at EOT and nine at FU96 (**Table 2**). Small decreases in HBV DNA were observed during bulevirtide treatment in patients taking concomitant NA medication (**Fig. S14**).

Liver-related clinical outcomes

Only one previously reported liver-related outcome, a nonserious case of ascites in a patient in the DT/bulevirtide 10 mg group, occurred during the treatment period (onset study W72).[9] From EOT through FU96, four patients experienced additional events (esophageal varices hemorrhage, ascites, hepatic encephalopathy, and hepatocellular carcinoma), one of which (ascites) was associated with posttreatment hepatitis D exacerbation (**Supplementary Results**).

Safety and tolerability

Adherence

Bulevirtide adherence rates were ≥93% in all groups. Further details are described in the **Supplementary Results**.

On-treatment safety

Table 3A summarizes on-treatment safety through EOT. Most AEs were mild or moderate in severity, with no study drug discontinuations due to AEs and no serious AEs (SAEs) or deaths that were attributed to bulevirtide through EOT. Dose-dependent elevations in total bile salt levels occurred during treatment, without associated

symptoms such as pruritus (**Fig. S15**). One unrelated AE that led to death was previously reported.[9] Further details are described in the **Supplementary Results**.

Posttreatment safety

Posttreatment ALT elevations >5 × ULN occurred in 57/140 (41%) patients; 14/140 (10%) experienced ALT elevations >10 × ULN, with similar frequencies across treatment groups (**Table 3B, Fig. S16**). Among patients with ALT >5 or >10 × ULN, 30/57 (53%) and 11/14 (79%), respectively, had cirrhosis at baseline, and 39/57 (68%) and 10/14 (71%) were on concomitant NA medication. Among the 69 patients with cirrhosis, 43% and 16% experienced flares of >5 or >10 × ULN, respectively. Most elevations occurred by FU24, were asymptomatic, and were associated with HDV rebound; 9/57 (16%) of ALT flares >5 × ULN and 2/14 (14%) of those >10 × ULN were associated with HBV reactivation. Overall, HBV reactivation occurred in 7/87 (8%) and 7/50 (14%) patients taking or not taking concomitant NA medication, respectively (**Table S5**). In most patients, ALT flares improved during follow-up, either spontaneously or with bulevirtide retreatment (**Fig. S17A**); corresponding HBsAg levels for these patients are shown in **Fig. S17B**. In the posttreatment period, 23/57 (40%) and 7/14 (50%) patients with ALT >5 or >10 × ULN, respectively, restarted commercial bulevirtide.

Overall, 20 patients experienced hepatic SAEs and 28 had hepatic Grade ≥3 AEs during the posttreatment period (**Table 3B**; **Table S6**). Posttreatment hepatic SAEs resolved in most (17/20 [85%]) patients: 16 of these patients restarted bulevirtide in the posttreatment period, and four patients were hospitalized posttreatment for liver-related

hepatic SAEs. Details on the three patients with unresolved hepatic SAEs are described in the **Supplementary Results.**

Discussion

We previously reported that bulevirtide 2 mg and 10 mg were superior to control at 48 weeks, with response rates improving through 96 weeks.[8,9] However, treatment outcomes beyond 2 years and after discontinuation of bulevirtide were unknown. Our results demonstrate that longer-term treatment with bulevirtide monotherapy through 144 weeks maintained efficacy compared with that at 96 weeks. Patients with suboptimal early virologic response benefitted from longer-term therapy, with many of these patients achieving virologic response by EOT. Rates of HDV RNA undetectability continued to improve over the third year of treatment. Furthermore, improvements in liver stiffness were especially pronounced in patients with cirrhosis. Only one liver-related event was observed throughout 3 years on treatment, consistent with the low rates of events in bulevirtide-treated patients from recent real-world bulevirtide data.[17]

This study is the first to present off-therapy data from the longest post-bulevirtide observation period reported to date. Virologic and biochemical response rates decreased after EOT, with viral rebound seen in most patients with detectable HDV RNA at EOT; however, some patients who achieved undetectable HDV RNA at EOT had sustained undetectability during posttreatment follow-up even in the presence of HBsAg. Sustained undetectable HDV RNA for 1 year posttreatment has been reported in some patients with CHD following 2 years of bulevirtide monotherapy.[15,18] After 2 to 3 years of bulevirtide monotherapy and 2 years of follow-up, some patients who achieved

undetectable HDV RNA at EOT had sustained undetectability off treatment, with no relapses observed in the second year of follow-up. In contrast, late relapses have been reported in up to 56% of patients following treatment with pegylated interferon,[19,20] occurring as late as 200 weeks posttreatment.[19] Thus, it is possible that late relapses may be observed with longer follow-up after discontinuation of bulevirtide. We used a stringent definition of sustained undetectability, requiring that all posttreatment HDV RNA measurements be below the detectable limit, which may mitigate this risk.

Patients with sustained undetectability maintained improvements in biochemical response during follow-up, while HDV rebound was associated with posttreatment ALT flares. This highlights the need to identify patients unlikely to relapse after discontinuing bulevirtide, as most patients benefit from continued therapy. The strongest predictor of sustained undetectability off treatment was the duration of continuous on-treatment undetectability at EOT; patients with ≥96 weeks of continuous undetectable HDV RNA at EOT were least likely to relapse. These data suggest the possibility that treatment may be discontinued in patients who achieve and maintain undetectable HDV on bulevirtide monotherapy for over 2 years, regardless of cirrhosis status.[18] However, further studies are needed to validate these findings, as most patients require continued bulevirtide therapy to maintain virologic and biochemical improvements and prevent liver disease progression. Additionally, the risk of posttreatment hepatitis flares after treatment discontinuation should be carefully considered, especially in patients with cirrhosis who may be at risk for more severe flares.

While combined response and biochemical response rates at EOT were similar across all treatment groups, the proportions of patients achieving undetectable HDV

RNA at EOT were greater in the groups that received bulevirtide 10 mg vs 2 mg, possibly reflecting more complete blockade of the NTCP receptor with bulevirtide 10 mg vs 2 mg.[21] In addition, bile salt elevations were more pronounced with the 10 mg dose, which may also indicate a greater degree of NTCP inhibition relative to the 2 mg dose. Previous data from bulevirtide-treated patients have demonstrated that reductions in serum HDV RNA are correlated with reductions in HDV-infected hepatocytes at W48, and that these serum HDV RNA reductions deepen with longer-term therapy.[22] In the current study, after fixed durations of treatment, the rates of undetectable HDV RNA at 96 weeks after EOT were similar between the bulevirtide 10 mg and 2 mg groups, reflecting the high rate of viral relapse in patients with a brief duration of undetectability at EOT. In real-world use, however, where treatment duration can be individualized based on response, the higher on-treatment rates of undetectable HDV RNA achieved with bulevirtide 10 mg could translate into higher numbers of patients able to discontinue bulevirtide with a low likelihood of viral relapse.

This study demonstrated that treatment with bulevirtide for up to 144 weeks was safe and well tolerated, and is associated with ongoing benefit in most patients. The posttreatment results should be interpreted in the context of the trial design but suggest that response-guided treatment decisions may be possible with future research. Hepatitis exacerbation following the cessation of effective antiviral treatment for HBV and HDV is well documented.[23-26] Hepatic SAEs and ALT elevations were observed in the posttreatment period and were often associated with HDV rebound; most hepatic SAEs resolved. Hepatic function should be closely monitored after bulevirtide discontinuation, especially in patients with cirrhosis, as retreatment may be necessary.

This study has several limitations. It used an open-label design, as placebo injections were deemed unethical; however, data integrity was preserved through objective laboratory-based measurements. The study population was predominantly White, with limited representation of other races. While not all HDV and HBV genotypes were included, bulevirtide has demonstrated potent in vitro activity against all recombinant HBV/HDV A–H/1–8 genotype combinations.[27] A substantial number of patients discontinued during follow-up, many due to HDV rebound requiring commercial bulevirtide retreatment, which, prior to a protocol amendment, was not permitted while remaining enrolled in the study. This limited the available data on posttreatment hepatitis flares and outcomes of bulevirtide retreatment. Additionally, the trial was underpowered to detect differences in HDV RNA undetectability between patients receiving bulevirtide 2 mg and 10 mg doses at W48 (key secondary endpoint). As an MEF statistical approach was used for binary efficacy endpoints, estimates of follow-up efficacy rates are conservative. Finally, not all patients received concomitant NAs; however, no impact on efficacy was observed.

In summary, treatment with bulevirtide monotherapy for up to 144 weeks in patients with CHD was safe, well tolerated, and effective, with improvements observed in combined, virologic, and biochemical responses, and continued increases in HDV RNA undetectability from 96 to 144 weeks of treatment. Higher rates of HDV RNA undetectability with bulevirtide 10 mg daily compared with bulevirtide 2 mg continued through EOT, although rates were similar at FU96. Of patients who achieved HDV RNA undetectability at EOT, a subset did not relapse through 2 years of follow-up, predicted by a longer duration of continuous on-treatment undetectability. In patients who

discontinue bulevirtide therapy, hepatic function should be monitored for at least 6 months due to the risk of hepatitis flares. Overall, virologic and biochemical response rates decreased after stopping bulevirtide, suggesting a clinical benefit of continued treatment in most patients.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AE, adverse event; ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; CHD, chronic hepatitis D; CR, combined response; DT, delayed treatment; EOT, end of treatment (study week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); FU96, follow-up at 96 weeks after EOT (week 240); IFN, interferon; ITT, intention-to-treat; LLOQ, lower limit of quantitation; MedDRA, Medical Dictionary for Regulatory Activities; MEF, missing-equals-failure; NA, nucleos(t)ide analogue; NTCP, sodium taurocholate cotransporting polypeptide; PT, preferred term; SAE, serious adverse event; s.c., subcutaneously; TND, target not detected; ULN, upper limit of normal; VR, virologic response; W, week.

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Tables

Table 1. Baseline demographics and disease characteristics.

	BLV 2 mg n = 49	BLV 10 mg n = 50	DT/BLV 10 mg n = 51*
Age, years, mean (SD)	44 (9)	41 (9)	41 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (51)
Race,† n (%)			
White	41 (84)	43 (86)	40 (78)
Asian	8 (16)	6 (12)	11 (22)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (47)
Liver stiffness, kPa, mean (SD)	14.0 (8.19)	14.8 (9.26)	15.3 (8.95)
ALT, U/L, mean (SD)	108 (63)	123 (81)	102 (62)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.10 (1.19)	4.96 (1.46)	5.08 (1.36)
Genotype HDV-1,‡ n (%)	49 (100)	48 (96)	51 (100)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.67 (0.52)	3.61 (0.59)	3.68 (0.47)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.31 (1.28)	1.08 (1.26)	0.89 (0.99)
HBV genotype,§ n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (86)
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
Concomitant HBV NA treatment, n (%)	32 (65)	27 (54)	33 (65)

*At baseline (randomization), 51 patients were assigned to DT/BLV 10 mg, and their data are reported here. One patient subsequently withdrew from the DT/BLV 10 mg group before receiving BLV and is not included in subsequent reporting of efficacy and safety. †BLV 10 mg arm: Black, n = 1. ‡BLV 10 mg arm: HDV genotype 5, n = 1; missing

HDV genotype, n = 1. [§]Other: BLV 10 mg arm: HBV genotype E, n = 1; no data, n = 3; DT/BLV 10 mg arm: unclassified HBV genotype, n = 2; no data, n = 3.

ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; IFN, interferon; NA, nucleos(t)ide analogue.

Table 2. Efficacy from EOT to FU96.

Patients, n (%)	BLV 2 mg n = 49			BLV 10 mg n = 50			DT/BLV 10 mg n = 50		
	EOT (144 weeks of BLV)	FU48	FU96	EOT (144 weeks of BLV)	FU48	FU96	EOT (96 weeks of BLV)	FU48	FU96
CR	28 (57)	11 (22)	12 (24)*	27 (54)	10 (20)	12 (24)*	28 (56)	9 (18)	12 (24)*
VR	36 (73)	14 (29)	16 (33)*	38 (76)	20 (40)*	15 (30)*	46 (92)	14 (28)	16 (32)†
ALT normalization	29 (59)	13 (27)	12 (24)*	30 (60)	14 (28)	16 (32)†	29 (58)	12 (24)	14 (28)*
Undetectable HDV RNA	14 (29)	8 (16)	10 (20)	25 (50)	12 (24)	11 (22)	26 (52)	8 (16)	10 (20)
HBsAg loss	0	1 (2)	1 (2)	0	1 (2)	1 (2)	1 (2)	1 (2)	2 (4)
HBsAg response	1 (2)	3 (6)	4 (8)	1 (2)	1 (2)	1 (2)	1 (2)	4 (8)	4 (8)*
Composite response	12 (24)	6 (12)	8 (16)	16 (32)	7 (14)	9 (18)	16 (32)	7 (14)	8 (16)

Intention-to-treat analysis. For missing values, the missing-equals-failure approach was used.

CR was defined as virologic response (undetectable HDV RNA or decrease by ≥2 $\log_{10}$ IU/mL from baseline) and biochemical response (ALT normalization). VR was defined as a patient with HDV RNA decline from baseline of ≥2 $\log_{10}$ IU/mL or HDV RNA undetectable. ALT normalization was defined as ALT ≤31 U/L for females and ≤41 U/L for males (Russian sites) and ALT ≤34 U/L for females and ≤49 U/L for males (all other sites). Undetectable HDV RNA was defined as HDV RNA less than the lower limit of quantitation (50 IU/mL; TND). HBsAg response was defined as an HBsAg decrease

from BLV baseline of ≥1 log_{10} IU/mL. Composite response was defined as HDV RNA undetectable (TND) combined with ALT normalization.

*Includes 1 responder who restarted BLV prior to the visit. †Includes 2 responders who restarted BLV prior to the visit.

ALT, alanine aminotransferase; BLV, bulevirtide; CR, combined response; DT, delayed treatment; EOT, end of treatment (study week 144); FU48, follow-up at 48 weeks after EOT (week 192); FU96, follow-up at 96 weeks after EOT (week 240); TND, target not detected; VR, virologic responder.

Table 3A. On-treatment safety summary.

Patients, n (%)	BLV 2 mg EOT n = 49	BLV 10 mg EOT n = 50	DT/BLV 10 mg W48 to EOT* n = 50
Any AE	48 (98)	48 (96)	46 (92)
Any AE related to BLV	27 (55)	37 (74)	23 (46)
Any Grade ≥3 AE	12 (24)	10 (20)	5 (10)
Any SAE	3 (6)	6 (12)	3 (6)
Any AE leading to withdrawal of BLV	0	0	0
AE leading to death	0	0	1 (2)†
Hepatic AEs	14 (29)	10 (20)	5 (10)
Hepatic AEs, Grade ≥3	0	0	0
Hepatic SAEs	0	0	0

Table 3B. Posttreatment safety summary.

Patients, n (%)	BLV 2 mg EOT to FU96 n = 46	BLV 10 mg EOT to FU96 n = 47	DT/BLV 10 mg EOT to FU96 n = 49
Hepatic AEs	23 (50)	25 (53)	24 (49)
Hepatic SAEs by PT	6 (13)	6 (13)	8 (16)
Esophageal varices hemorrhage	1 (2)	0	0
Hepatitis	0	0	1 (2)
Hepatitis D	4 (9)	4 (9)	2 (4)

Patients, n (%)	BLV 2 mg EOT to FU96 n = 46	BLV 10 mg EOT to FU96 n = 47	DT/BLV 10 mg EOT to FU96 n = 49
Hepatitis acute	1 (2)	0	0
Hepatic function abnormal	0	0	1 (2)
Liver injury	0	0	1 (2)
ALT increased	0	1 (2)	1 (2)
Transaminases increased	0	1 (2)	1 (2)
Chronic hepatitis B	0	0	1 (2)
Hepatic AEs, Grade ≥3	9 (20)	9 (19)	10 (20)
Death	0	0	0
ALT >5 × ULN	18/46 (39)	19/46 (41)	20/48 (42)
Cirrhosis at baseline	10/18 (56)	10/19 (53)	10/20 (50)
HDV rebound	11/18 (61)	15/19 (79)	17/20 (85)
HBV reactivation	4/18 (22)	1/19 (5)	4/20 (20)
Concomitant NA medication	14/18 (78)	11/19 (58)	14/20 (70)
ALT >10 × ULN	5/46 (11)	3/46 (7)	6/48 (13)
Cirrhosis at baseline	4/5 (80)	2/3 (67)	5/6 (83)
HDV rebound	3/5 (60)	3/3 (100)	4/6 (67)
HBV reactivation	0/5	0/3	2/6 (33)
Concomitant NA medication	5/5 (100)	1/3 (33)	4/6 (67)

Hepatic AEs were identified using MedDRA Search Term “Post-Treatment Hep D Flare Including Clinical Sequelae.” The denominator for ALT >5 × ULN and ALT >10 × ULN was the number of patients with ≥1 posttreatment ALT measurement. HDV rebound

was defined as an increase of HDV RNA ≥2 log_{10} IU/mL from the LLOQ of 50 IU/mL (if HDV RNA <LLOQ at EOT) or an increase of ≥2 log_{10} IU/mL posttreatment compared with the HDV RNA level at EOT. HBV reactivation was defined as any HBV reactivation AE term during the posttreatment period, a change from negative to positive HBsAg status during the posttreatment period, or any change meeting AASLD criteria for reactivation (if HBV DNA was undetectable at EOT, HBV DNA ≥3 log_{10} IU/mL; if HBV DNA was detectable at EOT, an increase of ≥2 log_{10} IU/mL during the posttreatment period).

*AEs from the first 48 weeks are not shown. †One AE that started during BLV treatment resulted in death after treatment discontinuation. The cause was plasma cell myeloma and was determined to be unrelated to the study drug..

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (study week 144); FU96, follow-up at 96 weeks after EOT (week 240); LLOQ, lower limit of quantitation; MedDRA, Medical Dictionary for Regulatory Activities; NA, nucleos(t)ide analogue; PT, preferred term; SAE, serious adverse event; ULN, upper limit of normal; W, week.

Figure legends

Fig. 1. Efficacy during therapy and posttreatment follow-up. Patients with missing values were considered nonresponders; 95% CIs were calculated based on the Clopper-Pearson exact method. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (study week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); FU96, follow-up at 96 weeks after EOT (week 240).

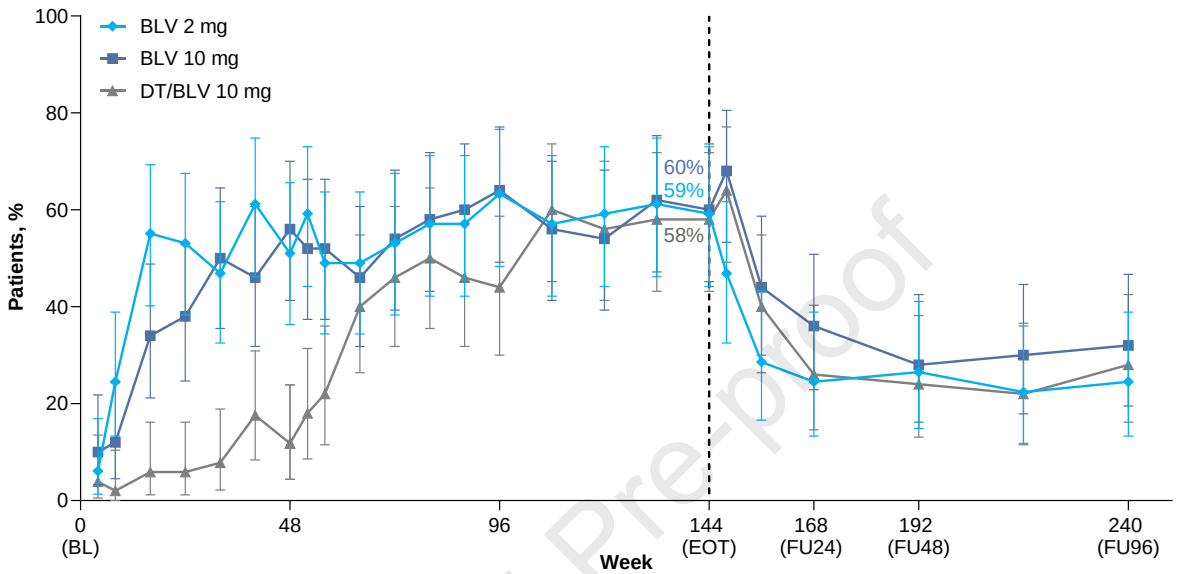
Fig. 2. Mean ALT (A) and HDV RNA (B) levels over time. Observed cases only; missing values were not imputed. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (study week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); FU96, follow-up at 96 weeks after EOT (week 240).

Fig. 3. Time of HDV RNA relapse (A) and duration of continuous on-treatment HDV RNA undetectability by relapse status (B). Only patients with HDV RNA undetectable at EOT and data demonstrating relapse or sustained undetectability at or after FU24 during follow-up are included. One patient in the BLV 2 mg group had no follow-up data. *Represents patients with HBsAg loss during the study. †Represents patients with <1 week of undetectable HDV RNA. BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (study week 144); FU24, follow-up at 24 weeks after EOT (week 168).

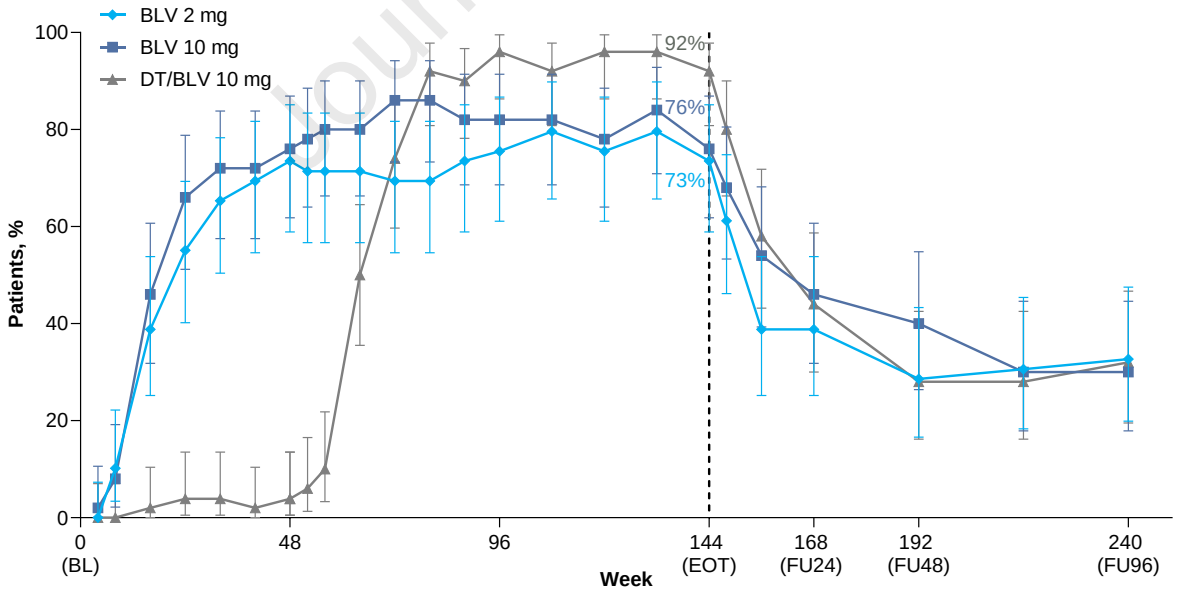
Figures

Fig. 1. Efficacy during therapy and posttreatment follow-up.

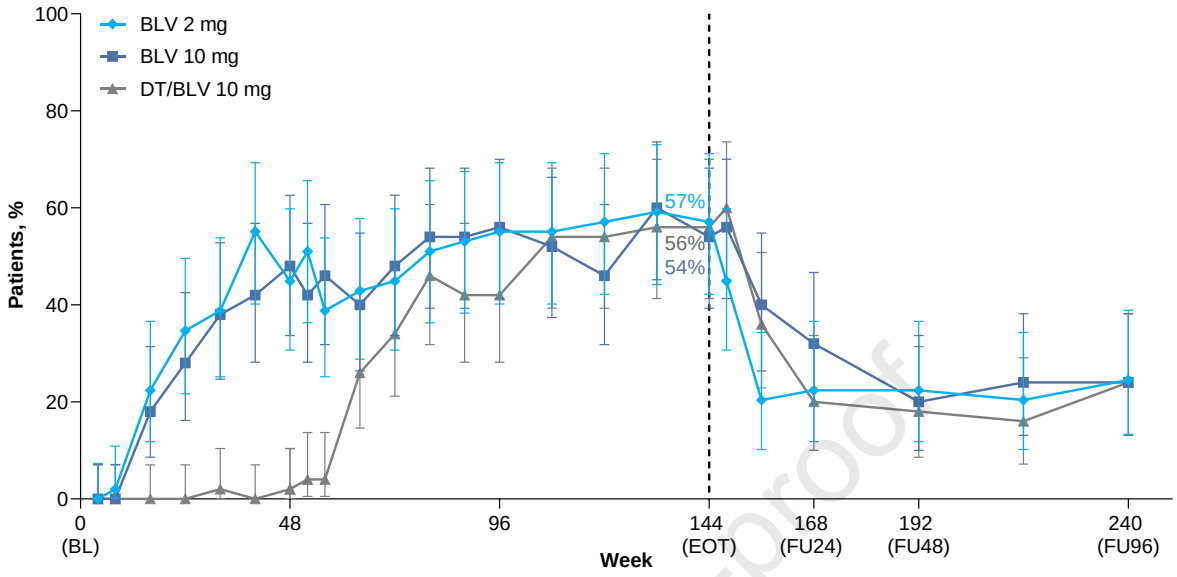
A. ALT normalization



B. Virologic response



C. Combined response



D. Undetectable HDV RNA

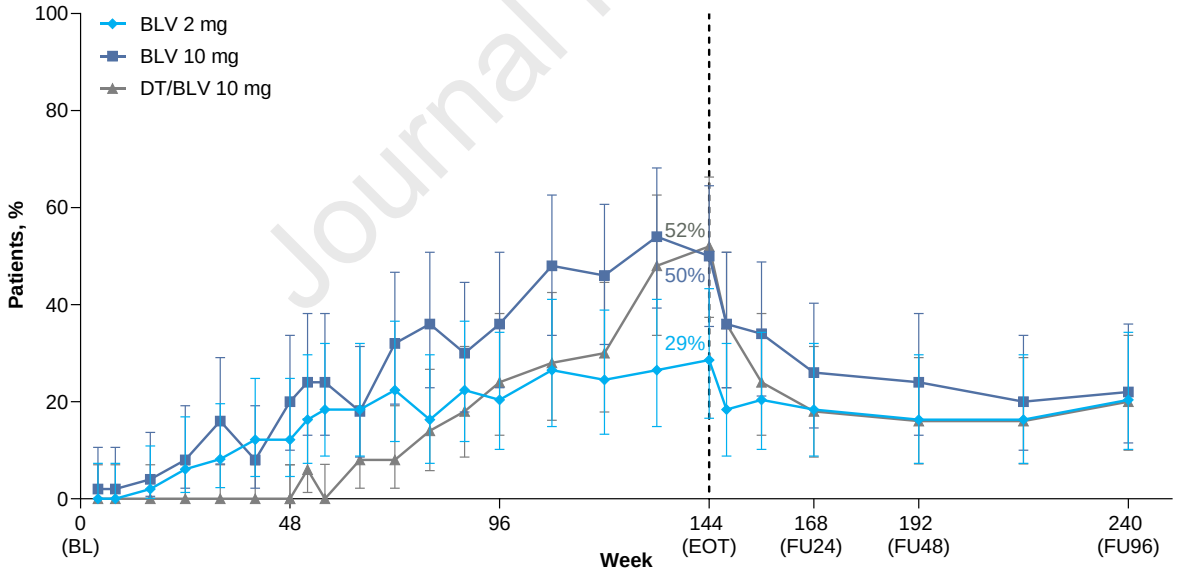
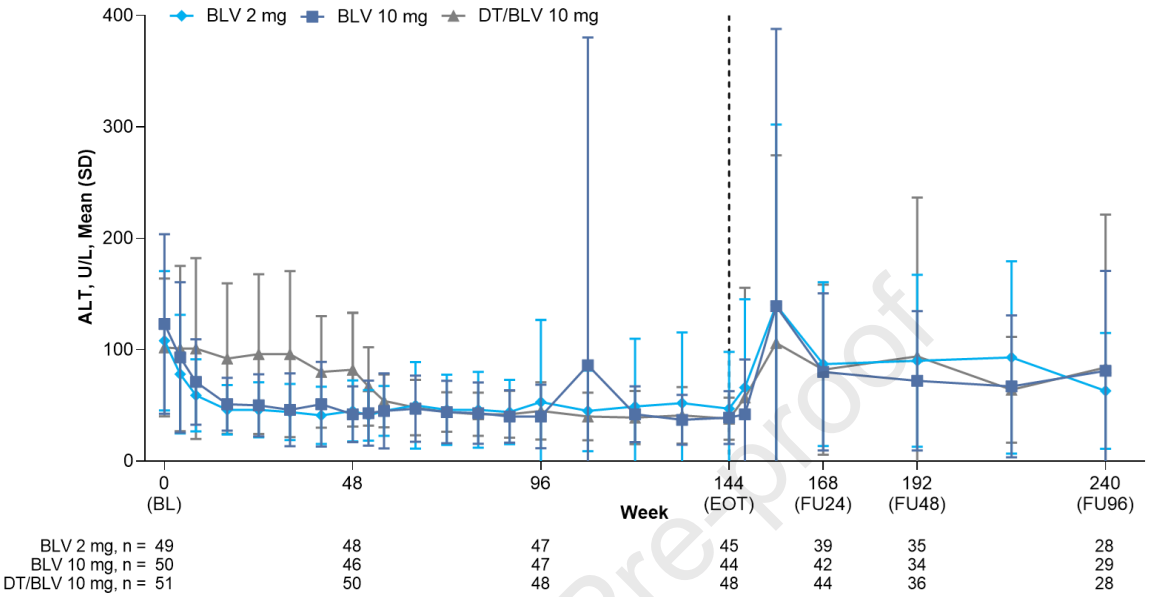


Fig. 2. Mean ALT (A) and HDV RNA (B) levels over time.

A. ALT



B. HDV RNA

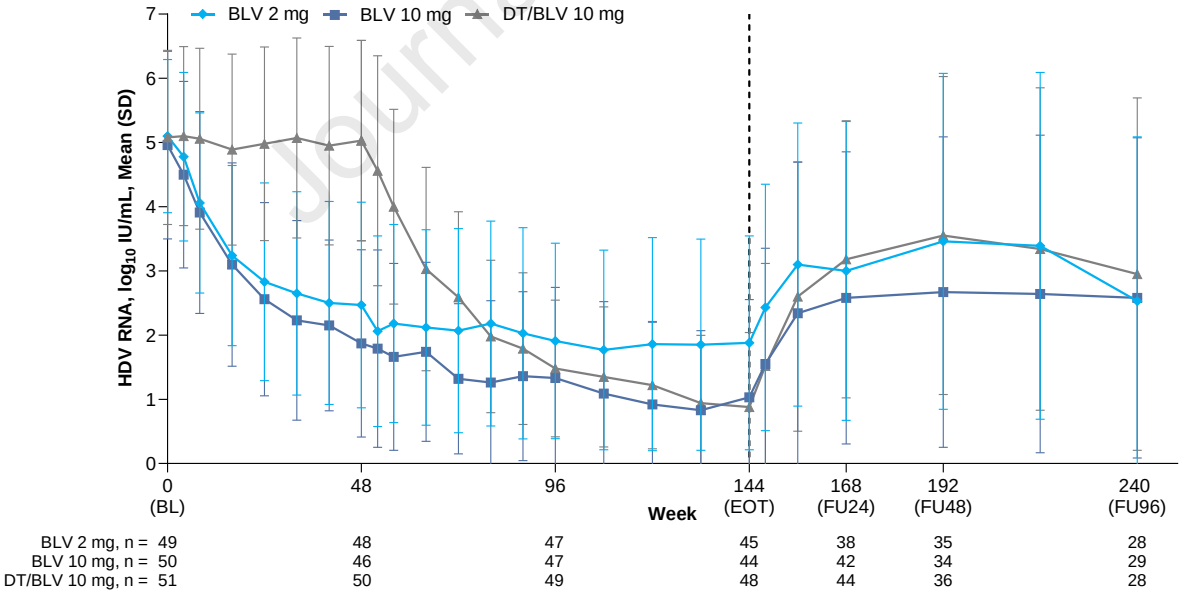
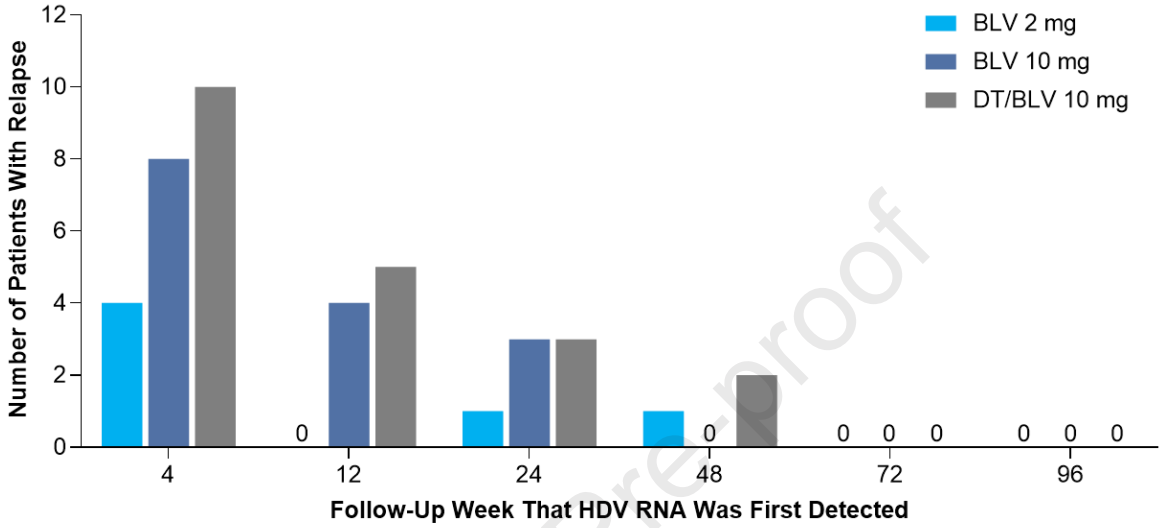
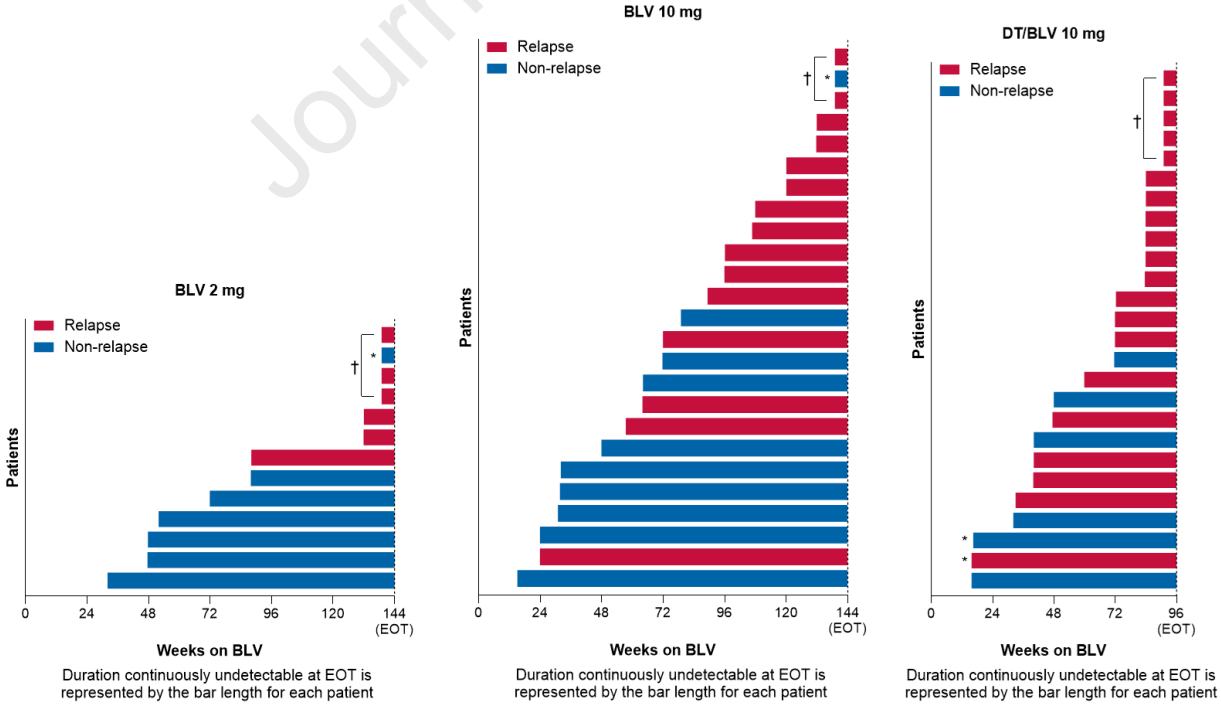


Fig. 3. Time of HDV RNA relapse (A) and duration of continuous on-treatment HDV RNA undetectability by relapse status (B).

A.



B.



Highlights

- Bulevirtide is well tolerated and effective through 144 weeks of treatment
- Virologic and biochemical response rates decreased posttreatment
- Some patients sustained undetectable HDV RNA through up to 2 years of follow-up
- These patients maintained improvements in biochemical response posttreatment
- Duration of continuous HDV RNA undetectability at EOT predicts sustained posttreatment undetectability