Characteristics and Outcomes of On-Treatment ALT Flares in Patients with Hepatitis Delta Virus Receiving Bulevirtide and Pegylated Interferon Alfa

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Fabien Zoulim[1], Soo Aleman[2], Tarik Asselah[3], Pavel Bogomolov[4], Maurizia Brunetto[5,6], Vladimir Chulanov[7], George Sebastian Gherlan[8,9], Pietro Lampertico[10,11], Viacheslav Morozov[12], Olga Sagalova[13], Tatiana Stepanova[14], Adrian Streinu-Cercel[15,16], Amos Lichtman[17], Mingyang Li[17], Danielle Shing[18], Shane Kelly[18], Steve Tseng[17], Dmitry Manuilov[17], Heiner Wedemeyer[19]

[1]INSERM Unité Mixte de Recherche 1350, PaThLiv IHU EVEREST, Université Claude-Bernard Lyon 1, 69003 Lyon, France; [2]Department of Infectious Diseases, Karolinska University Hospital/Karolinska Institutet, Stockholm, Sweden; [3]Hôpital Beaujon APHP, Université de Paris-Cité, INSERM UMR1149, Clichy, France; [4]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation; [5]Department of Clinical and Experimental Medicine, University of Pisa and Hepatology Unit, Pisa, Italy; [6]Reference Tuscany Center for Liver Disease and HCC, University Hospital of Pisa, Pisa, Italy; [7]Sechenov University, Moscow, Russian Federation; [8]Dr. Victor Babes Foundation, Bucharest, Romania; [9]University of Medicine and Pharmacy "Carol Davila" Bucharest, Bucharest, Romania; [10]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [11]CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [12]LLC Medical Company Hepatolog, Samara, Russian Federation; [13]South Ural State Medical University, Chelyabinsk, Russian Federation; [14]LLC Clinic of Modern Medicine, Moscow, Russian Federation; [15]National Institute of Infectious Diseases Prof. Dr. Matei Bals, Bucharest, Romania; [16]University of Medicine and Pharmacy "Carol Davila" Bucharest, Bucharest, Romania; [17]Gilead Sciences, Inc., Foster City, CA, USA; [18]Gilead Sciences International, Ltd., Cambridge, United Kingdom; [19]Clinic for Gastroenterology, Hepatology, Infectious Diseases, and Endocrinology, Hannover Medical School, Hannover, Germany

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Conclusions

- Compared with pegylated interferon alfa (PegIFNα) alone, treatment with bulevirtide (BLV) plus PegIFNα was associated with a numerically lower rate of on-treatment alanine aminotransferase (ALT) flares (28% vs 41%). Importantly, a substantially higher proportion of these flares were considered beneficial (85% vs 38%) and coincided with reductions in viral markers
- ALT flares during BLV + PegIFNα treatment generally self-resolved before end of treatment and were accompanied by a positive treatment response
- Safety outcomes observed with on-treatment flares were similar between BLV + PegIFNα and PegIFNα groups
- These findings suggest BLV may positively mediate on-treatment ALT flares potentially caused by PegIFNα

Plain Language Summary

- Alanine aminotransferase flares (temporary spikes in liver enzyme levels) during bulevirtide + pegylated interferon alfa treatment occurred less frequently than with pegylated interferon alfa alone
- The flares were generally temporary, resolved before treatment ended, and had a safety profile similar to pegylated interferon alfa alone
- Most of the on-treatment flares with bulevirtide + pegylated interferon alfa were considered beneficial to patients, as they were associated with decreases in hepatitis D virus or hepatitis B virus markers

References: **1.** Hepcludex. Prescribing information. United States Food and Drug Administration. Gilead Sciences, Inc.; 2026. **2.** Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2024. **3.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **4.** Hepcludex. Product monograph. Gilead Sciences Canada, Inc.; 2025. **5.** Wedemeyer H, et al. J Hepatol. 2026:S0168-8278(26)00201-1. **6.** Lampertico P, et al. Liver Int. 2025;45(2):e70008. **7.** Asselah T, et al. N Engl J Med. 2024;391(2):133-143. **8.** Hardtke S, et al. J Viral Hepat. 2025;32(4):e70022.

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Correspondence: Fabien Zoulim, fabien.zoulim@inserm.fr

Introduction

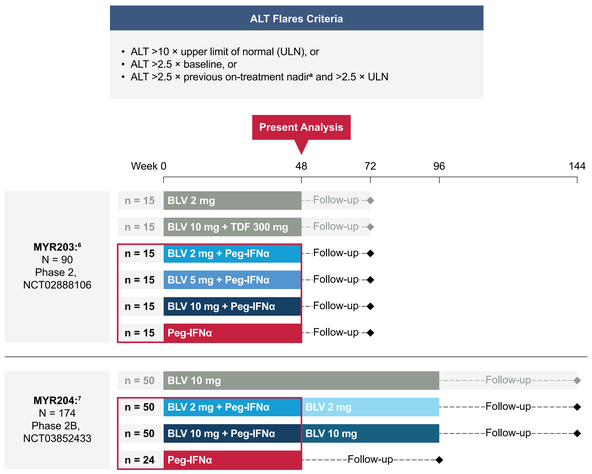
- Bulevirtide (BLV), a first-in-class entry inhibitor of hepatitis delta virus (HDV), is approved in the United States, the European Economic Area, and multiple other countries for the treatment of patients with chronic hepatitis delta (CHD) infection with compensated liver disease[1–4]
- BLV, either as monotherapy or in combination with pegylated interferon alfa (PegIFNα), has demonstrated virologic response (VR) and alanine aminotransferase (ALT) normalization in clinical trials[5–7]
- ALT flares can occur during PegIFNα therapy and may be beneficial in inducing a VR[8]
  - Currently, there is no single definition widely accepted for ALT flares in patients with HDV
- There are limited data about on-treatment ALT flares and outcomes for patients with CHD receiving BLV and PegIFNα

Objectives

- To evaluate on-treatment ALT flares occurring with BLV + PegIFNα vs PegIFNα monotherapy in patients with CHD

Methods

Figure 1. Study Designs



[a]Nadir was the lowest on-treatment ALT value previously recorded

ALT, alanine aminotransferase; BLV, bulevirtide; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- This pooled analysis included patients from two Phase 2 studies, MYR203 (NCT02888106) and MYR204 (NCT03852433), who received PegIFNα monotherapy or in combination with BLV 2, 5, or 10 mg (approved as 8.5 mg delivered dose in the United States)[1] for 48 weeks (**Figure 1**)[6,7]
  - The on-treatment period for this analysis ended at last dose of PegIFNα + 7 days for all groups
- Key inclusion criteria were:[6,7]
  - Adults with chronic HDV infection with or without compensated cirrhosis
  - ALT ≥1 x to <10 x ULN
  - Positive serum HDV RNA
- Beneficial flares were defined as either of the following occurring on or within 8 weeks of flare onset date:
  - HDV RNA newly undetectable or decline of >1 $\log_{10}$ IU/mL, or
  - Hepatitis B surface antigen (HBsAg) loss or decline of >0.5 $\log_{10}$ IU/mL

Results

Table 1. Demographics and Baseline Disease Characteristics

	BLV + PegIFNα (N = 145)	PegIFNα (N = 39)
Age, years, mean (SD)	40 (8.6)	38 (8.4)
Sex, male, n (%)	98 (67.6)	23 (59.0)
Race, n (%)		
Asian	8 (5.5)	5 (12.8)
Black or African American	5 (3.4)	0
White	131 (90.3)	34 (87.2)
Other	1 (0.7)	0
Body mass index, kg/m², mean (SD)	24.7 (3.9)	25.5 (4.2)
Cirrhosis present, n (%)	41 (28.3)	12 (30.8)
Liver stiffness, kPa, mean (SD)	12.5 (6.9)	14.0 (9.8)
ALT, U/L, mean (SD)	121 (168.6)	110 (79.9)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.4 (1.4)	5.1 (1.1)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.8 (0.7)	3.8 (0.5)
Previous IFN therapy, n (%)	55 (37.9)	16 (41.0)
Concomitant HBV NA treatment, n (%)	47 (32.4)	11 (28.2)

ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue; PegIFNα, pegylated interferon alfa.

- Demographics and baseline characteristics were generally similar between groups (**Table 1**)

Table 2. On-treatment ALT Flare Characteristics

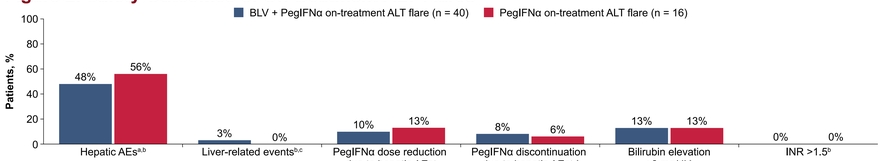
	BLV + PegIFNα (N = 145)	PegIFNα (N = 39)
On-treatment ALT flare by Week 48, n/N (%)	40/145 (28)	16/39 (41)
ALT >10 × ULN and >1 × baseline, n/N[a] (%)[b]	9/40 (23)	5/16 (31)
ALT >2.5 × baseline, n/N[a] (%)[b]	25/40 (63)	11/16 (69)
ALT >2.5 × nadir[c] and >2.5 × ULN, n/N[a] (%)[b]	29/40 (73)	12/16 (75)
On-treatment ALT flare onset, median (Q1, Q3), weeks	8 (4, 18)	14 (8, 20)
On-treatment ALT flares that resolved by Week 48, n/N[a] (%)	31/40 (78)	11/16 (69)

[a]N represents patients with on-treatment ALT flare by Week 48 (BLV + PegIFNα: 40; PegIFNα: 16). [b]In both treatment arms, ALT flare sub-categories were not mutually exclusive. [c]Nadir was the lowest on-treatment ALT value previously recorded.

ALT, alanine aminotransferase; BLV, bulevirtide; PegIFNα, pegylated interferon alfa; ULN, upper limit of normal.

- Of 184 patients, 56 (30%) had on-treatment ALT flares by Week 48: 28% (40/145) BLV + PegIFNα and 41% (16/39) PegIFNα (**Table 2**)

Figure 2. Safety Outcomes of On-treatment ALT Flares

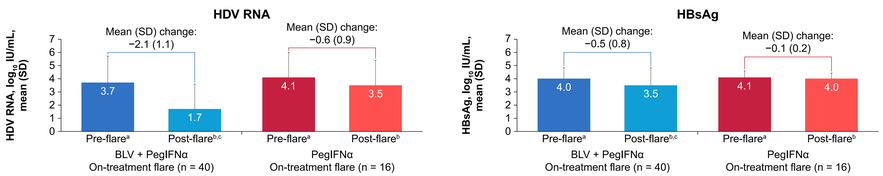


[a]Defined as AEs suggestive of hepatitis flares. [b]Safety outcomes are from on-treatment ALT flare onset up to Week 48 in the on-treatment period. [c]Defined as liver-related clinical events such as cirrhosis development; liver decompensation including development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy, bleeding from varices, and liver failure; HCC development; liver transplantation and liver related death. [d]Includes discontinuation due to drug-induced liver injury.

AE, adverse event; ALT, alanine aminotransferase; BLV, bulevirtide; HCC, hepatocellular carcinoma; INR, international normalized ratio; PegIFNα, pegylated interferon alfa.

- Overall, similar safety outcomes of on-treatment ALT flares were observed by Week 48 between the BLV + PegIFNα and PegIFNα groups (**Figure 2**)
- In the BLV + PegIFNα group there was one on-treatment liver-related event of hepatic cirrhosis without decompensation

Figure 3. Efficacy Outcomes Pre- and Post- On-treatment ALT Flares



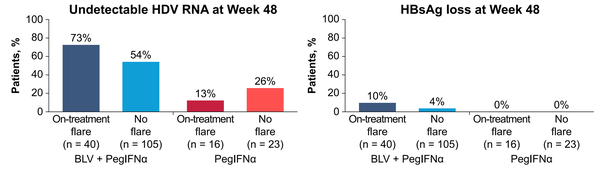
Bars represent mean values; upper error bars represent +1 standard deviation.

[a]The pre-flare value was defined as the last value prior to flare onset. [b]Post-flare value was defined as the last value on or within subsequent 8 weeks of flare onset in the on-treatment period by Week 48. [c]n = 39.

BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa.

- Pre-flare, mean HDV RNA and HBsAg values were similar between BLV + PegIFNα and PegIFNα groups with on-treatment ALT flares (**Figure 3**)
- Post-flare, larger mean decreases in HDV RNA and HBsAg were observed for patients receiving BLV + PegIFNα compared with PegIFNα

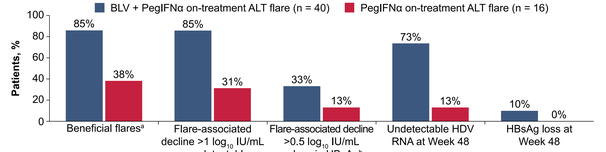
Figure 4. Efficacy Outcomes at Week 48 for Patients With and Without On-treatment ALT Flares



BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa.

- Patients receiving BLV + PegIFNα with on-treatment ALT flares had higher rates of HDV RNA undetectability and HBsAg loss at Week 48 versus patients without flares (**Figure 4**)
- This trend was not observed in the PegIFNα monotherapy group, although interpretation is limited due to small sample size in this group

Figure 5. Characteristics of Beneficial Flares

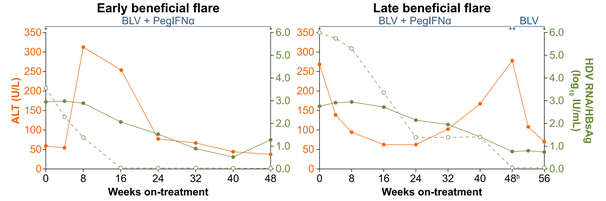


[a]Beneficial flares were defined as an HDV RNA newly undetectable or decline of >1 $\log_{10}$ IU/mL or HBsAg loss or decline of >0.5 $\log_{10}$ IU/mL on or within subsequent 8 weeks of flare onset in the on-treatment period by Week 48. [b]On or within 8 weeks of flare onset in the on-treatment period by Week 48.

ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa.

- For patients with on-treatment ALT flares, a larger proportion in the BLV + PegIFNα group had a beneficial flare by Week 48 compared with the PegIFNα group (**Figure 5**)
  - Larger proportions of the BLV + PegIFNα group also had beneficial outcomes of undetectable or a decline in HDV RNA, or a loss or decline in HBsAg compared with the PegIFNα group

Figure 6. Representative Case Reports[a] for Early and Late Beneficial Flares on BLV 10 mg + PegIFNα



Last visit shown is at Week 48 or resolution of the flare, whichever came last.

[a]Case reports selected from MYR204. [b]Treatment with PegIFNα ends at Week 48.

ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa.

- Representative case reports for early and late on-treatment beneficial ALT flares may self-resolve and/or have resolution coinciding with PegIFNα withdrawal and be accompanied by a positive treatment response regardless of when the flare occurred (**Figure 6**)