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Poster for you

48-Week Off-Therapy Efficacy and Safety of Bulevirtide in Combination With Pegylated Interferon Alfa-2a in Patients With Chronic Hepatitis Delta: Final Results from the Phase 2b, Open-Label, Randomised, Multicentre Study MYR204

Tarik Asselah[1], Vladimir Chulanov[2], Pietro Lampertico[3,4], Heiner Wedemeyer[5], Adrian Streinu-Cercel[6,7], Victor Pântea[8], Stefan Lazar[9], Gheorghe Placinta[8], George Sebastian Gherlan[7,10], Pavel Bogomolov[11], Tatyana Stepanova[12], Viacheslav Morozov[13], Vladimir Syutkin[14], Olga Sagalova[15], Vladimir Gorodin[16], Dmitry Manuilov[17], Renee-Claude Mercier[17], Lei Ye[17], Grace Chee[17], Ben L. Da[17], Audrey H. Lau[17], Anu Osinusi[17], Marc Bourliere[18], Vlad Ratziu[19], Stanilas Pol[20], Marie-Noëlle Hilleret[21], Fabien Zoulim[22]

[1]Hôpital Beaujon APHP, Université de Paris-Cité, INSERM UMR1149, Clichy, France; [2]Sechenov University, Moscow, Russian Federation; [3]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; [4]CRC "A. M. and A. Migliavacca" Centre for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [5]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany; [6]Matei Bals National Institute of Infectious Diseases; [7]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [8]Infectious Clinical Hospital "T. Ciorba," Chisinau, Moldova; [9]Dr. Victor Babes Foundation, Infectious and Tropical Diseases Hospital, Bucharest, Romania; [10]Dr. Victor Babes Foundation, Bucharest, Romania; [11]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation; [12]LLC Clinic of Modern Medicine, Moscow, Russian Federation; [13]LLC Medical Company "Hepatolog," Samara, Russian Federation; [14]Institute of Emergency Medicine n.a. NV Sklifosovsky, Moscow, Russian Federation; [15]South Ural State Medical University, Chelyabinsk, Russian Federation; [16]"Specialized Clinical Infectious Diseases Hospital," Krasnodar, Russian Federation; [17]Gilead Sciences Inc, Foster City, CA, USA; [18]Hôpital Saint Joseph, Marseille, France; [19]CH Pitié-Salpêtrière, Paris, France; [20]Hôpital Cochin, Paris, France; [21]Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; [22]Hospital Croix Rousse, Lyon, France.

Conclusions

In this MYR204 study of finite treatment for CHD:

- BLV 10 mg in combination with PegIFNα achieved:
  - — Highest rates of HDV RNA undetectability, which were maintained at 24 and 48 weeks after EOT
  - — Superiority to BLV 10 mg monotherapy at 24 and 48 weeks after EOT
- Improvements in liver stiffness at 48 weeks after EOT observed in the combination groups
- HBsAg loss was infrequent but observed in the combination groups
- BLV combined with PegIFNα had a similar safety profile as the individual drug components; post-treatment ALT increases were observed but were mostly asymptomatic and transient
- **BLV in combination with PegIFNα provides a novel opportunity for finite CHD treatment**

Introduction

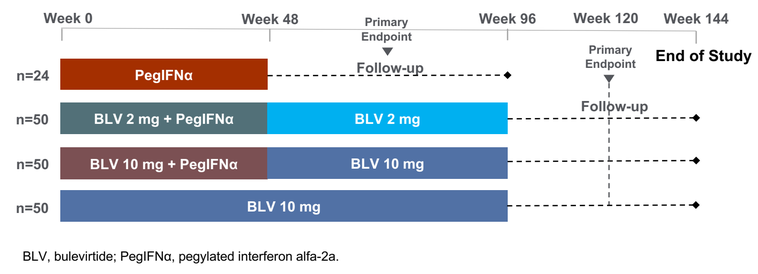
- Hepatitis delta virus (HDV) is a satellite virus, requiring the envelope protein from hepatitis B virus (HBV) to infect hepatocytes[1]
- Between 10 and 20 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis[3,4] and has a 2- to 3-fold increased risk of mortality compared to HBV moninfection[5,6]
- Pegylated interferon alfa-2a (PegIFNα) has been recommended as off-label therapy for chronic hepatitis delta (CHD), has low rates of sustained undetectable HDV RNA post-therapy, and has high rates of relapse[7]
- Bulevirtide (BLV) 2 mg is a first-in-class entry inhibitor fully approved in the EU, Great Britain, Switzerland, Australia, and the Russian Federation for the treatment of adults with CHD and compensated liver disease[8-10]

Objective

- To evaluate the safety and efficacy of finite treatment with BLV (2 mg and 10 mg) with or without pegylated interferon alfa-2a (PegIFNα) in patients with compensated CHD at 48 weeks after end of treatment

Methods

Figure 1 **Study Design**



BLV, bulevirtide; PegIFNα, pegylated interferon alfa-2a.

- Open-label, randomised, multicentre, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key inclusion criteria

- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh ≤6
- Alanine aminotransferase (ALT) >1 × to <10 × upper limit of normal (ULN); platelets >90,000 cells/mm^3
- No IFN within 6 months before enrolment

Primary endpoint

- HDV RNA undetectable at 24 weeks after end of treatment (EOT)
  - — HDV RNA levels determined by RT-qPCR using RoboGene HDV RNA Quantification Kit 2.0 (lower limit of quantification [LLOQ] 50 IU/mL, lower limit of detection 6 IU/mL), undetectable HDV RNA defined as less than the LLOQ, target not detected
- The primary efficacy analysis was the difference between the BLV 10 mg + PegIFNα group vs BLV 10 mg monotherapy group

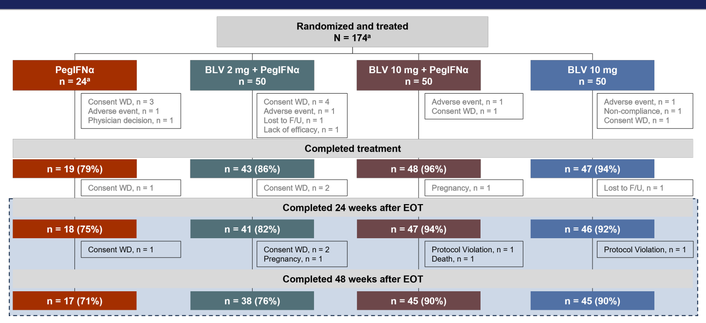
Secondary endpoints at 48 weeks after EOT

- Undetectable HDV RNA
- Change from baseline in liver stiffness
- Safety

Additional endpoints at 48 weeks after EOT

- ALT normalisation
  - — ALT within normal ranges as established by the testing laboratory
- Composite response: undetectable HDV RNA and ALT normalisation
  - — As recommended by US FDA: Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance, November 2019

Figure 2 **Patient Disposition**



[a]One patient in PegIFNα arm was randomised but not treated.
BLV, bulevirtide; EOT, end of treatment; F/U: follow-up; PegIFNα, pegylated interferon alfa-2a; WD, withdrawal.

Results

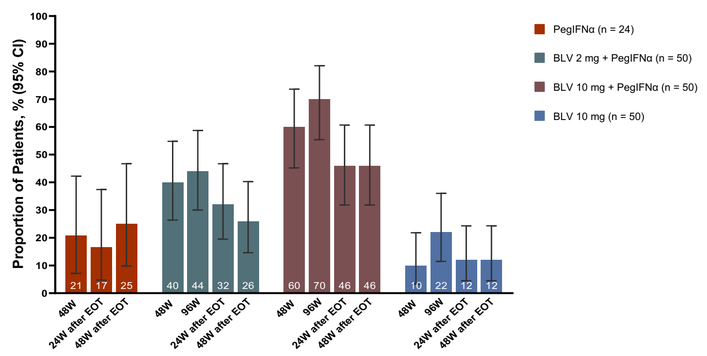
Table 1 **Baseline Demographics and Disease Characteristics**

		PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
Mean age, years (SD)		41 (8.4)	41 (9.3)	41 (8.6)	40 (8.5)
Male sex, n (%)		18 (75)	33 (66)	35 (70)	38 (76)
Race[a], n (%)	Caucasian	20 (83)	44 (88)	43 (86)	44 (88)
	Asian	4 (17)	3 (6)	4 (8)	4 (8)
	Black	0	3 (6)	2 (4)	2 (4)
Cirrhosis, n (%)		8 (33)	17 (34)	17 (34)	17 (34)
Median liver stiffness, kPa (Q1, Q3)		12.2 (8.6, 18.9)	10.7 (7.8, 16.5)	10.5 (7.8, 14.3)	10.8 (8.5, 14.1)
Median ALT, U/L (Q1, Q3)		91 (64, 152)	81 (56, 143)	82 (55, 117)	90 (63, 127)
Median HDV RNA, log_{10} IU/mL (Q1, Q3)		5.2 (4.6, 5.8)	5.6 (4.3, 6.3)	5.5 (4.4, 6.1)	5.6 (4.6, 6.3)
HDV GT[b], 1/5/6, n (%)		24 (100)/0/0	48 (96)/1 (2)/ 1 (2)	47 (94)/2 (4)/0	49 (98)/1 (2)/0
Mean HBsAg, log_{10} IU/mL (SD)		3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
Mean HBV DNA, log_{10} IU/mL (SD)		1.4 (1.1)	1.7 (1.6)	1.5 (1.1)	1.8 (1.6)
HBV DNA ≥10 IU/mL, n (%)		9 (38)	23 (46)	21 (42)	24 (48)
HBeAg negative, n (%)		23 (96)	42 (84)	47 (94)	43 (86)
HBV GT[b], A/D/E, n (%)		4 (17)/19 (79)/ 0	7 (14)/40 (80)/ 1 (2)	7 (14)/38 (76)/ 2 (2)	8 (16)/42 (84)/ 0
Prior interferon use, n (%)		12 (50)	25 (50)	26 (52)	21 (42)
Concomitant HBV medication, n (%)		11 (46)	24 (48)	25 (50)	23 (46)

[a]PegIFNα + BLV 10 mg: n=1 other race. [b]Only available/classified data presented. ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PegIFNα, pegylated interferon alfa-2a; Q, quartile.

- The baseline demographics were well-balanced between the arms.

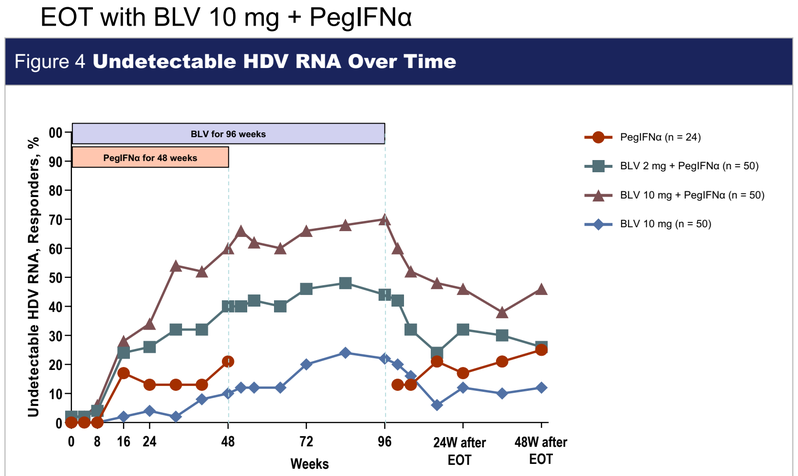
Figure 3 **Undetectable HDV RNA at 48 Weeks After EOT**



Missing = failure. BLV, bulevirtide; EOT, end of treatment; PegIFNα, pegylated interferon alfa-2a; W, weeks.

- Response rates were highest at 46% with BLV 10 mg + PegIFNα
- Response rates were maintained between 24 and 48 weeks after EOT with BLV 10 mg + PegIFNα

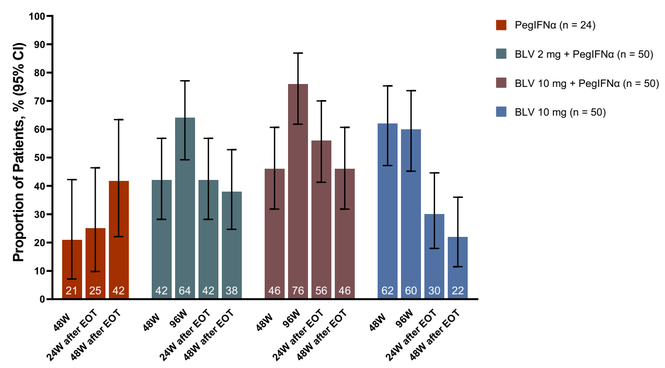
Figure 4 **Undetectable HDV RNA Over Time**



Missing = failure. BLV, bulevirtide; EOT, end of treatment; PegIFNα, pegylated interferon alpha

- In the combination arms, the response rates continually increased throughout the treatment period including after PegIFNα was stopped at 48 weeks
- Response rates were generally maintained in all arms between 24 and 48 weeks after EOT

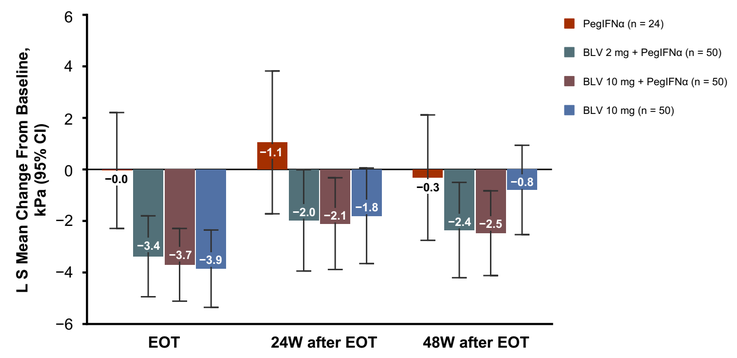
Figure 5 **ALT Normalisation at 48 Week After EOT**



Missing = failure. ALT, alanine aminotransferase; BLV, bulevirtide; EOT, end of treatment; PegIFNα, pegylated interferon alfa-2a.

- The proportion of patients with ALT normalisation increased in all treatment arms
- Higher rates of ALT normalisation were observed in all PegIFNα treatment arms compared to BLV monotherapy at 48 week after EOT

Figure 6 **Liver Stiffness: Change From Baseline**



Liver stiffness as measured by FibroScan (elasticity). MMRM model including treatment assignment, region, presence of cirrhosis, visit and treatment-by-visit interaction as fixed-effect factors and baseline liver stiffness as covariate. BLV, bulevirtide; EOT, end of treatment; LS, least squares; PegIFNα, pegylated interferon alfa-2a.

- Similar improvements in liver stiffness were observed at 48 weeks after EOT in the combination arms

Table 2 **HBsAg Endpoints at 48 Week After EOT**

		PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
HBsAg	HBsAg response[a]: ≥1 log_{10} decrease IU/mL, n (%)	4 (17)	11 (22)	8 (16)	2 (4)
	HBsAg loss[a], n (%)	0	5 (10)	2 (4)	1 (2)
	with seroconversion[a], n (%)	0	4 (8)	2 (4)	0
	Mean change from BL in HBsAg, log_{10} IU/mL (SD)	n = 17 −0.51 (0.705)	n =34 −1.39 (1.847)	n = 43 −0.72 (1.072)	n = 44 −0.24 (0.772)

[a]Missing = failure. BL, baseline; BLV, bulevirtide; EOT, end of treatment; HBsAg, hepatitis B surface antigen; PegIFNα, pegylated interferon alfa-2a.

- HBsAg loss was observed with BLV 2 mg or 10 mg in combination with PegIFNα

Table 3 **On-Treatment Safety**

Treatment-Emergent Adverse Events, n (%)	PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
Any AE	22 (92)	49 (98)	50 (100)	42 (84)
Any Grade ≥3 AE related to BLV	N/A	2 (4)	2 (4)	0
Any Grade ≥3 AE related to PegIFNα	13 (54)	26 (52)	26 (52)	N/A
Any SAE	3 (13)	3 (6)	8 (16)	2 (4)
Any SAE related to BLV	N/A	0	0	0
Any SAE related to PegIFNα	1 (4)	2 (4)	1 (2)	N/A
Any AE leading to D/C of study treatment	1	3 (6)	2 (4)	1 (2)
BLV related AE leading to D/C of study treatment	N/A	0	0	1 (2)[a]
Death	0	1 (2)[b]	0	0

[a]BLV 10 mg: Myalgia related to BLV (Grade 2, nonserious). [b]Anaplastic astrocytoma not related to study treatment. AE, adverse event; BLV, bulevirtide; D/C, discontinuation; EOT, end of treatment; HBsAg, hepatitis B surface antigen; N/A, not applicable; PegIFNα, pegylated interferon alpha; SAE, serious adverse event.

- Safety profile observed with BLV and PegIFNα was consistent with the known safety profile of each drug
- Few Grade 3 TEAEs related to BLV, no SAE related to BLV

Table 4 **Posttreatment Safety**

Adverse Event, n (%)	PegIFNα (n = 24)	BLV 2 mg + PegIFNα (n = 50)	BLV 10 mg + PegIFNα (n = 50)	BLV 10 mg (n = 50)
Any adverse event	19 (79)	28 (56)	29 (58)	34 (68)
Grade ≥3	2 (8)	4 (8)	10 (20)	11 (22)
Serious adverse event	1 (4)	2 (4)	4 (8)	4 (8)
Related to bulevirtide[a]	N/A	1 (2)	1 (2)	1 (2)
All deaths[b]	0	0	1 (2)[†]	0
Posttreatment hepatic AEs, overall	4 (17)	8 (16)	10 (20)	19 (38)
Posttreatment hepatic events in >1 patient				
ALT increased	3 (13)	8 (16)	5 (10)	14 (28)
AST increased	1 (4)	7 (14)	5 (10)	11 (22)
GGT increased	1 (4)	1 (2)	1 (2)	5 (10)
Bilirubin increased[c]	0	0	3 (6)	5 (10)
Jaundice	0	0	0	2 (4)
Prothrombin level decreased	0	0	1 (2)	1 (2)

[a]Posttreatment BLV related SAEs were jaundice, hepatocellular carcinoma and trisomy 21 with atrial septal defect; [b]Death related to esophageal varices hemorrhage; [c]Included terms blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and urobilinogen urine increased. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BLV, bulevirtide; GGT, gamma glutamyltransferase; N/A, not applicable; PegIFNα, pegylated interferon alpha.

- No BLV-related SAEs were observed on treatment
- Most ALT and AST elevations were asymptomatic, associated with HDV RNA rebounds, and transient

References: 1. Asselah T, Rizzetto M. *N Eng J Med*. 2023;389:58-70. **2.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **3.** Alfaiate D, et al. *J Hepatol*. 2020 Sep;73(3):533-539. **4.** Rizzetto M, et al. *J Hepatol*. 2021;74(5):1200-1211. **5.** Fattovich G, et al. *Gut*. 2000;46:420-6. **6.** Wranke A, et al. *Hepatol Int*. 2023 Oct 3; doi: 10.1007/s12072-023-10575-0. **7.** Sandmann L, et al. *Liver Int*. 2022;00:1-11. **8.** Hepcludex. European Medicines Agency SmPC. Gilead Sciences, Inc.; 2023. **9.** European Association for the Study of the Liver. *J Hepatol*. 2023;79:433-60. **10.** Hepcludex. Australian Register of Therapeutic Goods. Gilead Sciences, Inc. 2024. **Acknowledgments:** We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences. **Disclosures: TA** acted as a speaker and investigator for AbbVie; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; Janssen; Merck; MYR Pharmaceutical; and Roche. **PL** reports speaking and teaching fees from and participation in advisory committees or review panels for AbbVie; Aligos; Alnylam; Antios; Arrowhead; Bristol Myers Squibb; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; GSK; Janssen; Merck Sharp & Dohme; MYR GmbH; Roche; and Spring Bank Pharmaceuticals. **HW** reports honoraria for speaking or consulting from Abbott; AbbVie; Boehringer Ingelheim; Bristol Myers Squibb; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; Janssen; Merck Sharp & Dohme; MYR GmbH; Novartis; Novira; Roche; Roche Diagnostics; Siemens; and Transgene; and research support from Abbott; Bristol Myers Squibb; Gilead Sciences, Inc.; Novartis; Roche; and Roche Diagnostics. **VC** reports consultant and sponsored lecture fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Gilead Sciences, Inc., GSK, Hepatera, Merck Sharp & Dohme, Roche, and R-Pharm. **MB** reports being a board member and speaker for AbbVie; Gilead Sciences, Inc.; Intercept; and Roche. **VR** reports consultancy fees from Boehringer Ingelheim. **FZ** received consulting fees from Aligos; Antios; Assembly Biosciences; Gilead Sciences, Inc.; and GSK; and research funding to INSERM from Assembly Biosciences, Beam, and Janssen. **BLD**, **AO**, **DM**, **RCM**, **GC**, **AHL**, and **LY** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **ASC**, **VP**, **SL**, **GP**, **GSG**, **PB**, **TS**, **VM**, **VS**, **OS**, **VG**, **SP** and **MNH** report no conflicts of interest.