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#1063

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[12], Pietro Lampertico[3,4], Heiner Wedemeyer[5], Adrian Streinu-Cercel[6,9], Victor Pantea[7], Stefan Lazar[8], Gheorghe Placinta[7], George Sebastian Gherlan[9,10], 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" Center 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]Infectious Clinical Hospital "T. Ciorba," Chisinau, Moldova; [8]Dr. Victor Babes Foundation, Infectious and Tropical Diseases Hospital, Bucharest, Romania; [9]"Carol Davila" University of Medicine and Pharmacy, 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.

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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.

Background

- Hepatitis delta virus (HDV) is a satellite virus, requires the envelope protein from hepatitis B virus (HBV) to infect hepatocytes[1]
- Between 10-20 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis[3,4]
  - 2–3-fold increased risk of mortality compared to HBV mono-infection[5,6]
- Pegylated interferon-alfa (PegIFNα) recommended as off-label therapy for chronic hepatitis delta (CHD)
  - Low rates of sustained undetectable HDV RNA post-therapy and high rates of relapse[7]
- Bulevirtide (BLV), 2 mg, is a first-in-class entry inhibitor fully-approved in Europe for the treatment of adults with CHD and compensated liver disease
- **Objective:** To evaluate the safety and efficacy of finite treatment with BLV (2 mg and 10 mg) with or without pegylated interferon alfa-2a (PegIFN) in patients with compensated CHD at 48 week after end of treatment

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 International 2022;00:1-11.

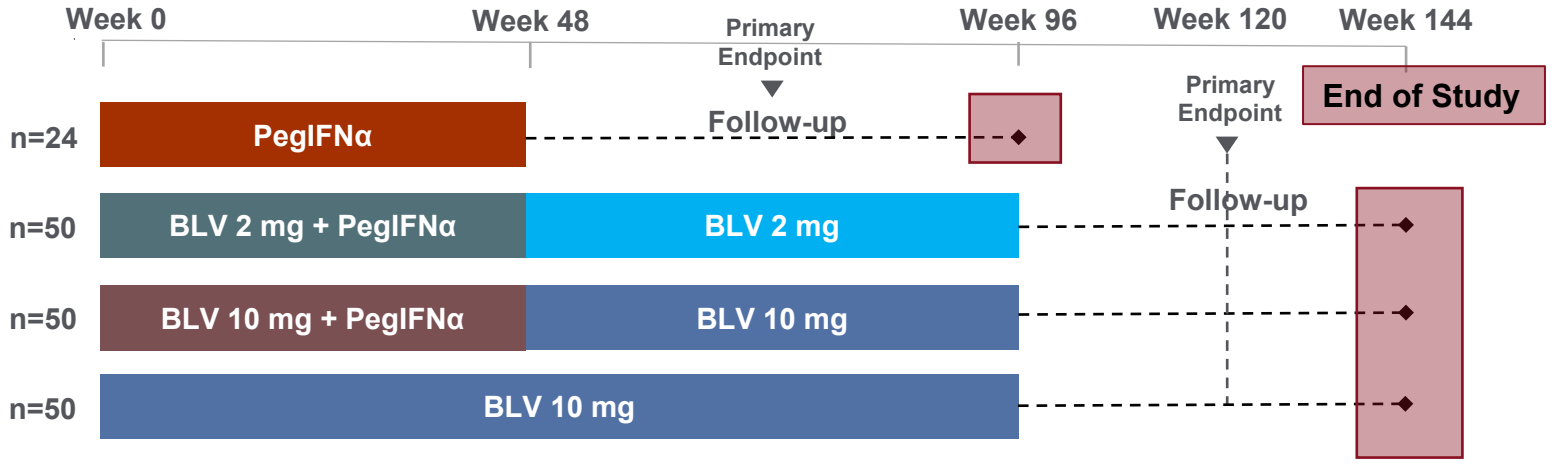
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D

T. Asselah, V. Chulanov, P. Lampertico, H. Wedemeyer, A. Streinu-Cercel, V. Pântea, S. Lazar, G. Placinta, G.S. Gherlan, P. Bogomolov, T. Stepanova, V. Morozov, V. Syutkin, O. Sagalova, D. Manuilov, R.-C. Mercier, L. Ye, B.L. Da, G. Chee, A.H. Lau, A. Osinusi, M. Bourliere, V. Ratziu, S. Pol, M.-N. Hilleret, and F. Zoulim

Study Design



- Open-label, randomized, multicenter, 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 (CTP) ≤6
- ALT >1× - <10× ULN; Platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrollment

ALT, alanine transaminase; **BLV**, bulevirtide; **CHD**, chronic hepatitis D; **IFN**, interferon; **PegIFNα**, pegylated interferon alpha; **ULN**, upper limit of normal.

Study Endpoints

Primary endpoint:

- HDV RNA undetectable* at 24 Week after EOT
- The primary efficacy analysis was the difference between the BLV 10 mg + PegIFNα group vs BLV 10 mg monotherapy group

Secondary Endpoints at 48 Week after EOT :

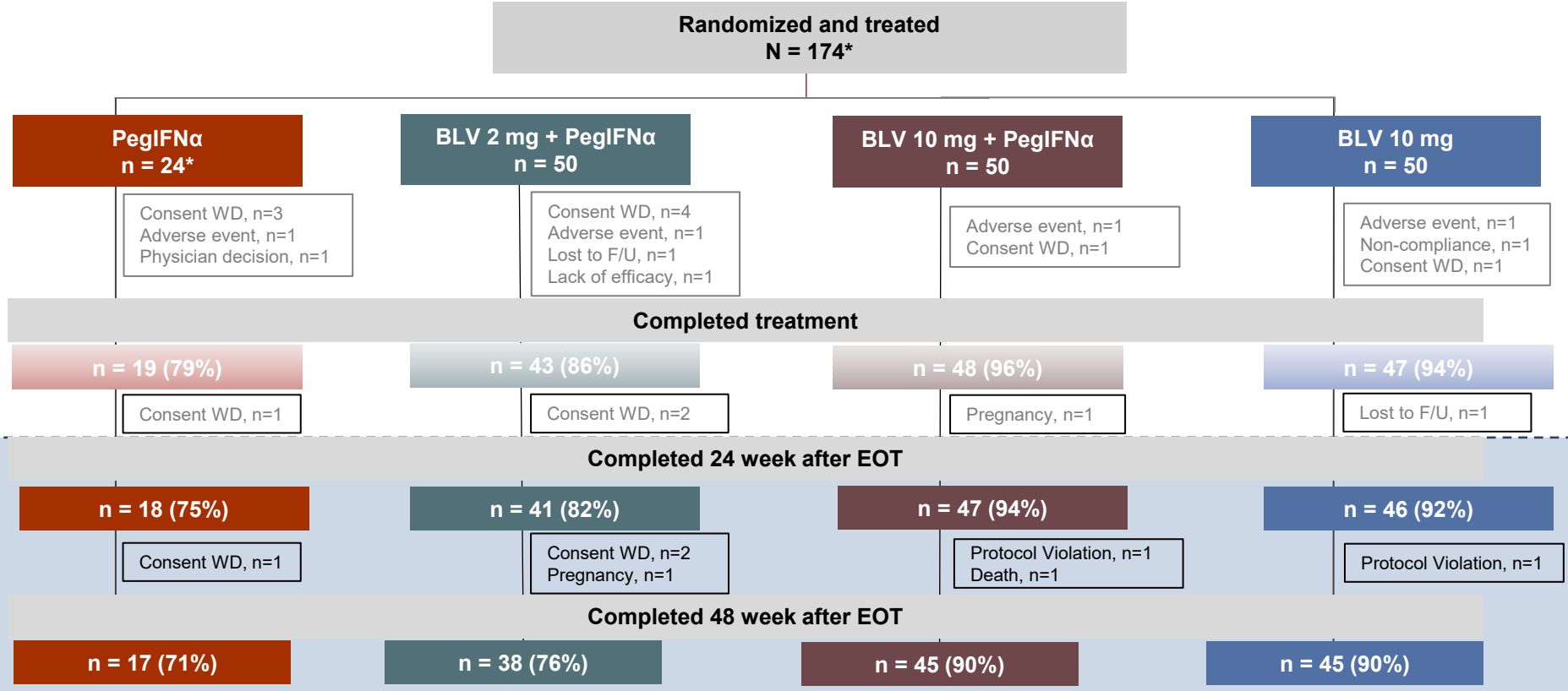
- Undetectable HDV RNA
- Change from baseline in liver stiffness
- Safety

Additional Endpoints at 48 Week after EOT:

- ALT normalization
- Composite response[a]: undetectable HDV RNA and ALT normalization

*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 <LLOQ, target not detected.
ALT within normal ranges as established by the testing laboratory; [a]As recommended by: Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance November 2019. **ALT**, alanine transaminase; **BL**, baseline; **BLV**, bulevirtide; **EOT**, end of treatment; **LLOQ**, lower limit of quantification; **PegIFNα**, pegylated interferon alpha.

Patient Disposition



*one patient in PegIFNa arm was randomized but not treated. **BLV**, bulevirtide; **F/U**: follow-up; **PegIFNα**, pegylated interferon alpha; **WD**, withdrawal; **EOT**, end of treatment.

Baseline Demographics & Disease Characteristics

		PegIFNα n = 24	PegIFNα + BLV 2 mg n = 50	PegIFNα + BLV 10 mg n = 50	BLV 10 mg n = 50
Mean age, y (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 $\geq$10 IU/mL, n (%)		17 (71)	41 (82)	38 (76)	40 (80)
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 (4)	8 (16) / 41 (82) / 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)

- The baseline demographics were well-balanced between the arms

[a]PegIFNα + BLV 10 mg: n=1 Other race; [b]Only available/classified data presented. **ALT**, alanine transaminase; **BLV**, bulevirtide; **GT**, genotype; **HBsAg,** hepatitis B surface antigen; **HBV**, hepatitis B virus; **PegIFNα**, pegylated interferon alpha; **Q**, quartile; **SD**, standard deviation; **y**, years.

Baseline Demographics & Disease Characteristics

		PegIFNα n = 24	PegIFNα + BLV 2 mg n = 50	PegIFNα + BLV 10 mg n = 50	BLV 10 mg n = 50
Mean age, y (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[#], 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)
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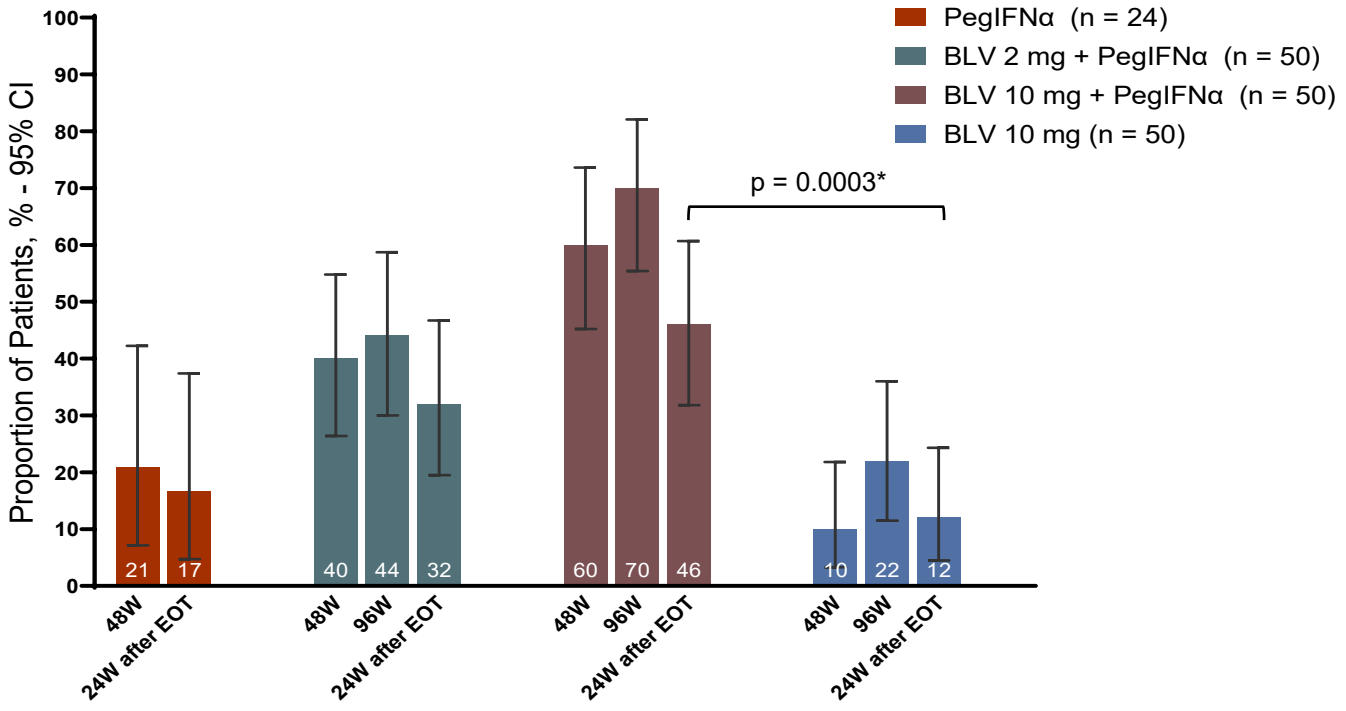
Median HDV RNA, $\log_{10}$ IU/mL (Q1, Q3)		5.2 (4.6, 5.8)	5.6 (4.3, 6.3)	5.5 (4.4, 6.1)	5.6 (4.6, 6.3)
HDV GT[b]- 1/ 5/ 6, n (%)		24 (100) /0 / 0	48 (96) / 1 (2) / 1 (2)	47 (94) / 2 (4) / 0	49 (98) / 1 (2) / 0
Mean HBsAg, $\log_{10}$ IU/mL (SD)		3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
Mean HBV DNA, $\log_{10}$ 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 transaminase; **BLV**, bulevirtide; **GT**, genotype; **HBsAg,** hepatitis B surface antigen; **HBV**, hepatitis B virus; **PegIFNα**, pegylated interferon alpha; **Q**, quartile; **SD**, standard deviation; **y**, years.

Undetectable HDV RNA at 24 Week after EOT

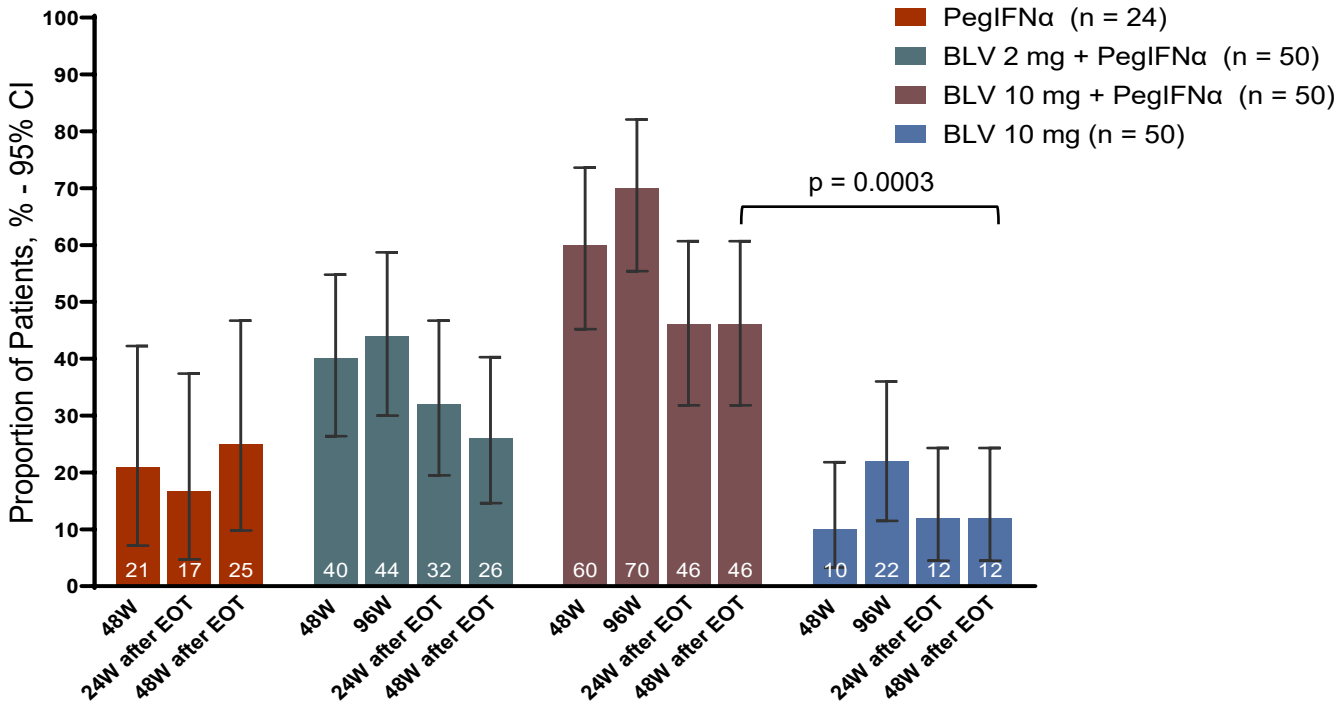


- Significantly higher rates were observed with BLV 10 mg + PegIFNα vs. BLV 10 mg at 24 week after EOT

AASLD 2023 Oral #5009; ***Primary endpoint; missing = failure. CI,** confidence interval; **W,** weeks; **BLV**, bulevirtide; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha

Undetectable HDV RNA at 48 Week after EOT

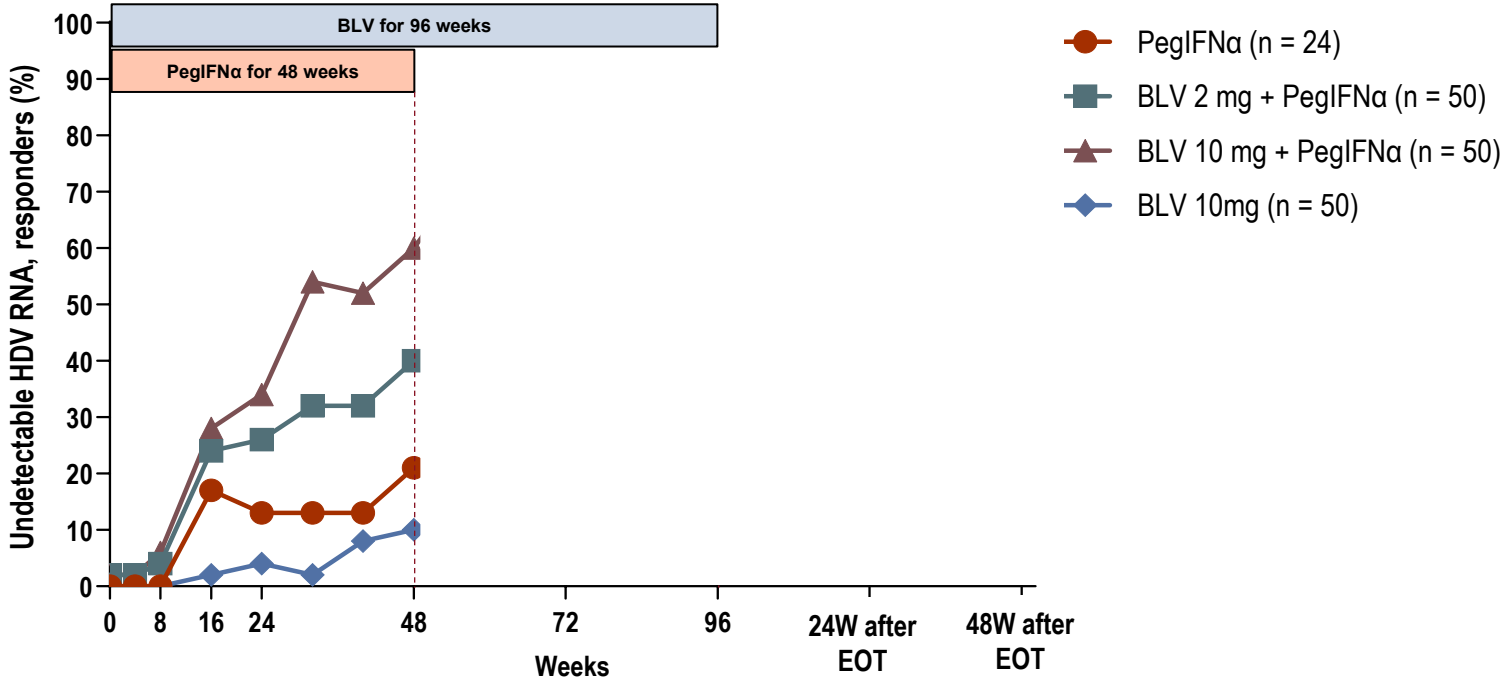
Undetectable HDV RNA at 48 Week after EOT



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

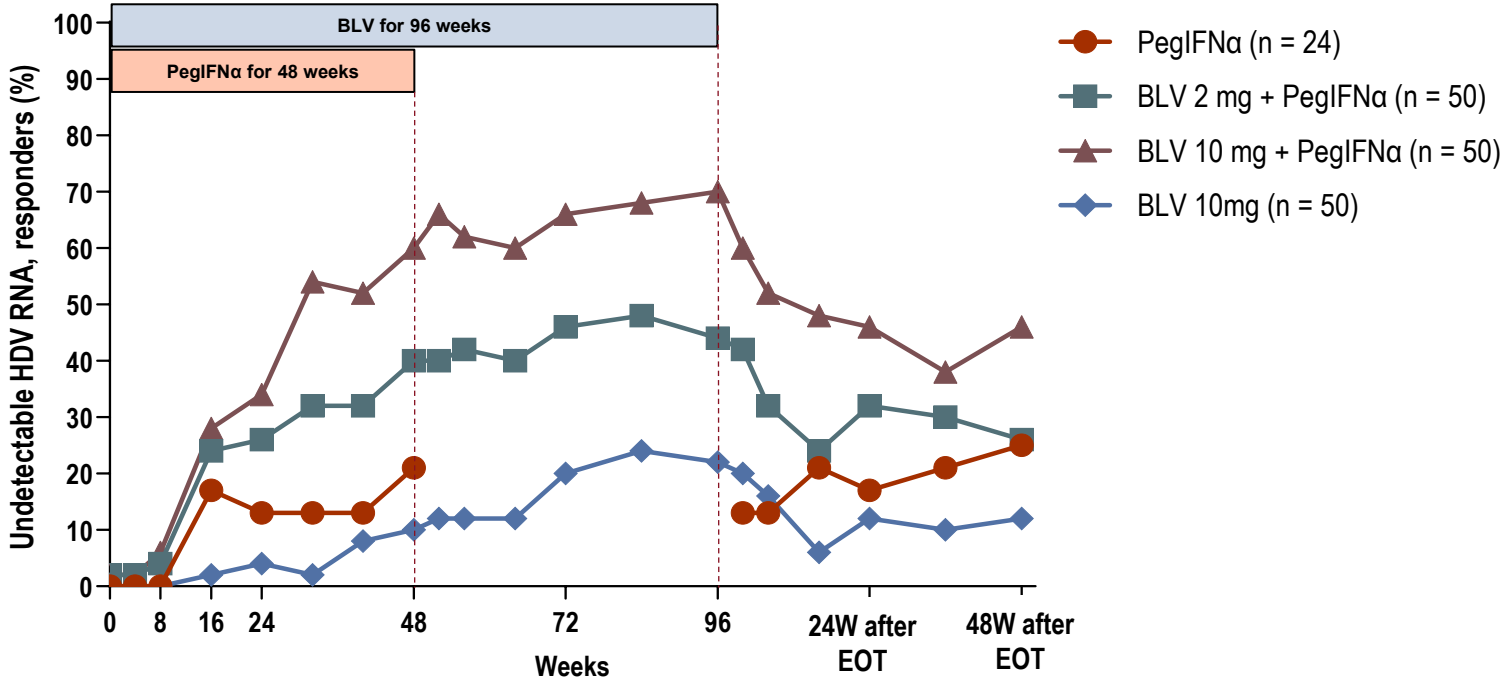
Missing = failure. CI, confidence interval; **W,** weeks; **BLV**, bulevirtide; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha

Undetectable HDV RNA Over Time



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

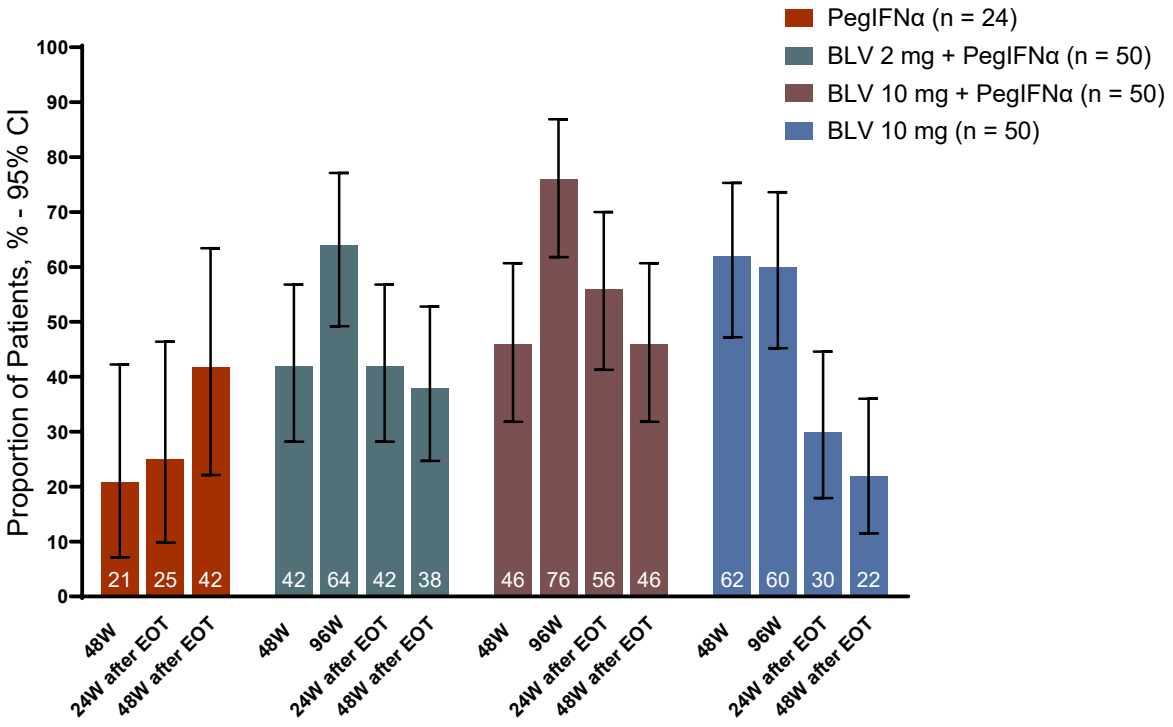
Undetectable HDV RNA Over Time



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

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

ALT Normalization at 48 Week after EOT

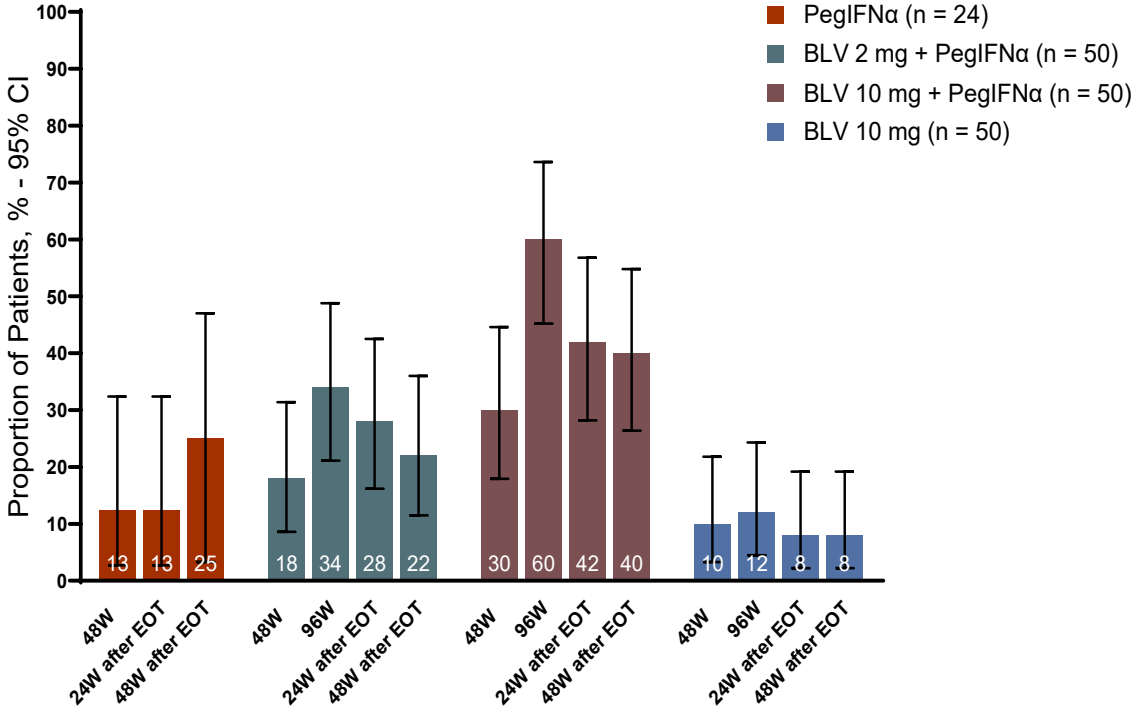


- The proportion of patients with ALT normalization increased in all treatment arms
- Higher rates of ALT normalization were observed in all PegIFNα treatment arms compared to BLV monotherapy at 48 week after EOT

Missing = failure. ALT, alanine transaminase; **BLV**, bulevirtide; **CI**, confidence interval; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha.

Composite Response at 48 Week after EOT

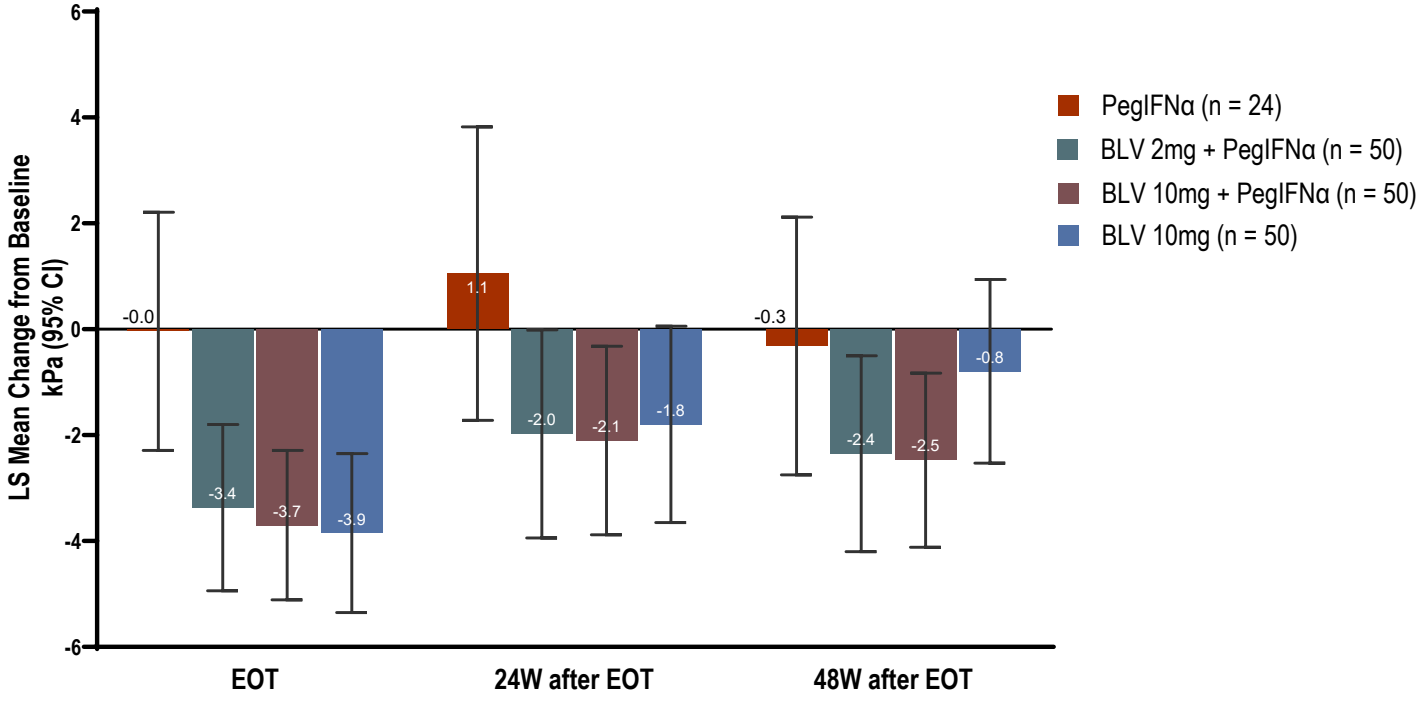
HDV RNA Undetectable + ALT Normalization



- BLV 10 mg + PegIFNα provided sustained composite response at 24 week and 48 week after EOT

Missing = failure. ALT, alanine transaminase; **BLV**, bulevirtide; **CI**, confidence interval; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha.

Liver Stiffness: Change from Baseline



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

*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; **CI**, confidence interval; **EOT**, end of treatment; **LS**, least squares; **PegIFNα**, pegylated interferon alpha.

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*: ≥1 $\log_{10}$ decrease IU/mL, n (%)	4 (17)	11 (22)	8 (16)	2 (4)
	HBsAg loss*, n (%)	0	5 (10)	2 (4)	1 (2)
	with seroconversion*, 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)

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

***Missing = failure. BL**, baseline; **BLV**, bulevirtide; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **PegIFNα**, pegylated interferon alpha; **SD**, standard deviation.

Additional Posters - MYR204

Abstract #1276, WED-395

"Undetectable HDV RNA Defined as Target Not Detected at the End of Treatment With Bulevirtide and/or Pegylated Interferon Alpha-2a Is an Important Predictor of 48 Weeks Sustained Virologic Response in Chronic Hepatitis Delta"

- Session: Viral Hepatitis B and D: Current therapies, Wednesday, June 5
- Viral Hepatitis Track Hub Poster tour, Friday June 7 16:15 – 17:00

Abstract #2778, FRI-371

"Undetectable HDV RNA at 24 weeks of treatment with bulevirtide and peginterferon alpha-2a combination therapy is an important predictor of maintained response off-therapy"

- Session: Viral Hepatitis B and D: Clinical Aspects, Friday, June 7

On-Treatment Safety

Treatment-Emergent Adverse Events, no (%)	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 3-4 AE related to BLV	N/A	2 (4)	2 (4)	0
Any Grade 3-4 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)[#]
Death	0	1 (2)^	0	0

- 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

[#]BLV 10 mg: Myalgia related to BLV (Grade 2, non-serious); ^Anaplastic astrocytoma not related to study treatment. **AE**, adverse event; **BLV**, bulevirtide; **D/C,** discontinuation; **EOT,** end of treatment; **N/A,** not applicable; **PegIFNα**, pegylated interferon alpha; **SAE**, serious adverse event.

Post-Treatment Safety

Adverse event, no (%)	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*	NA	1 (2)	1 (2)	1 (2)
All deaths	0	0	1 (2)†	0
Posttreatment hepatic adverse events - Overall	4 (17)	8 (16)	10 (20)	19 (38)
(shown below are those 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*	0	0	3 (6)	5 (10)
Jaundice	0	0	0	2 (4)
Prothrombin level decreased	0	0	1 (2)	1 (2)

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

* Post-treatment BLV related SAEs were jaundice, hepatocellular carcinoma and trisomy 21 with atrial septal defect; †Death related to esophageal varices hemorrhage; *Included terms blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and urobilinogen urine increased; **BLV**, bulevirtide; **PegIFNα**, pegylated interferon alpha; **NA**, not applicable; **ALT**, alanine aminotransferase; **AST,** aspartate aminotransferase; **GGT,** gamma glutamyltransferase.

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 week after EOT
  - Superiority to BLV 10 mg monotherapy at 24 and 48 week after EOT
- Improvements in liver stiffness at 48 week after EOT observed in the combination groups
- HBsAg loss were infrequent but observed in the combination groups
- BLV combined with PegIFNα had similar safety profile as individual drug component; post-treatment ALT increases were observed but mostly asymptomatic and transient

BLV in combination with PegIFN provides a novel opportunity for finite CHD treatment

ALT, alanine aminotransferase; BLV, bulevirtide; CHD, chronic hepatitis D; EOT, end of treatment; HBsAg, hepatitis B surface antigen; PegIFNα: pegylated interferon alpha.

Acknowledgements

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