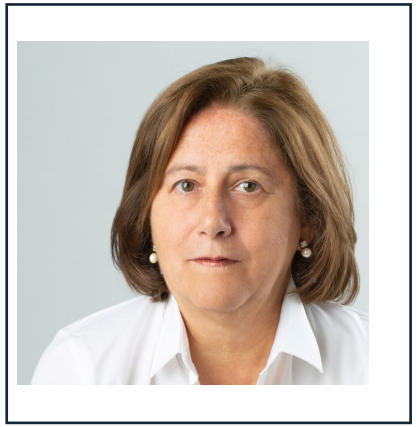
Maria Buti



Country: Spain

Affiliation: Hospital Universitario Valle Hebron

Function: Professor of Medicine

Main expertise: Viral Hepatitis B , D and C Diagnosis and THerapy

Treatment of Chronic Hepatitis D

Maria Buti, Barcelona, Spain

Maria Buti, MD Barcelona, Spain

UAB
Universitat Autònoma de Barcelona

Vall d'Hebron
Barcelona Campus Hospitalari

ciber | EHD

Disclosure of Conflicts of Interest

Declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Maria Buti

- Speaker and advisory fees and grants from Gilead.
- Speaker and advisory fees from AbbVie, Janssen, Altimmune, GSK and Vir.

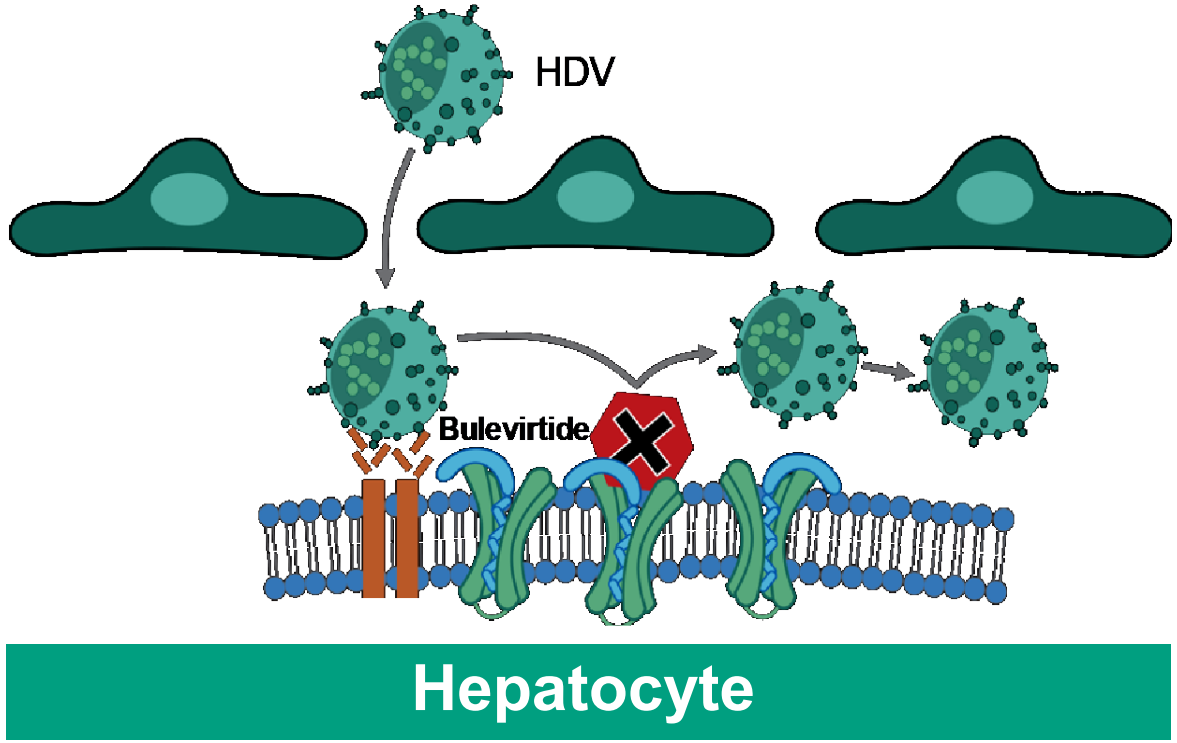
Hepatitis D

- 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]

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.

Bulevirtide

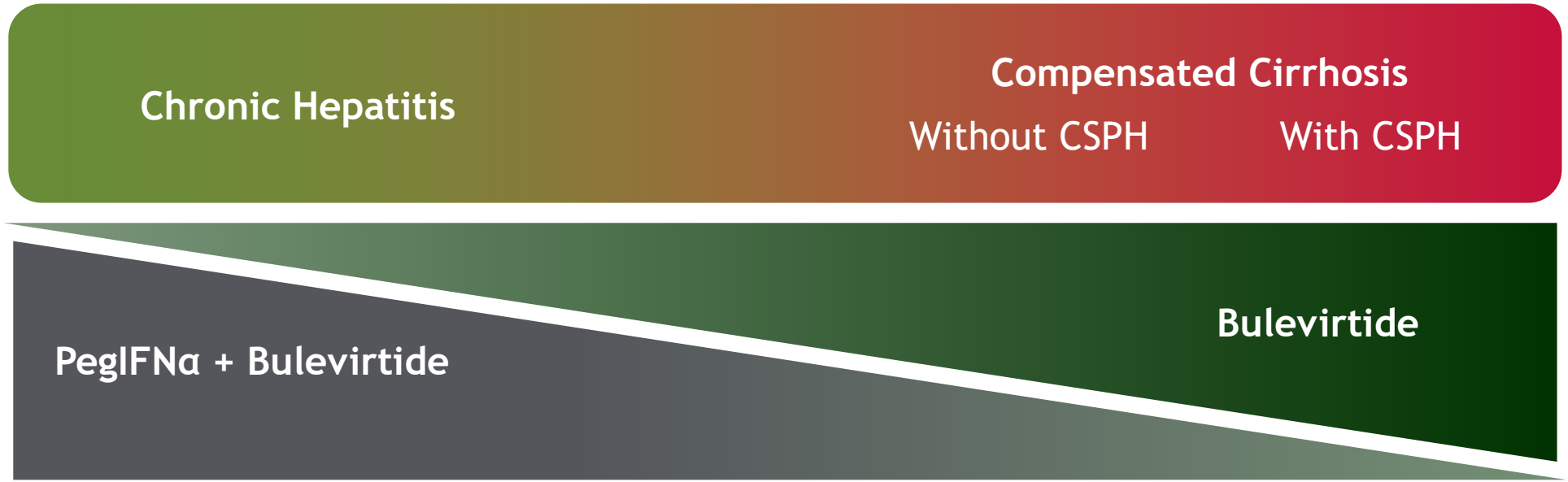
- A 47-aminoacid chemically synthesized lipopetic is an entry inhibitor for HBV and HDV[1,2]
- It binds to and blocks the surface protein of hepatocytes, NTCP, which is the entry receptor of HBV/HDV, preventing HDV from entering hepatocytes
- Bulevirtide is not an antiviral, it doesn't act directly by inhibiting HDV replication in infected cells
- The mechanism of action increases bile acids (NTCP is also a bile acid receptor)
- Subcutaneous injection daily[3]



BLV 2 mg/day is approved for the treatment of compensated CHD in the European Union, the United Kingdom, Switzerland, the Russian Federation and Australia

HDV: Hepatitis Delta Virus; HBV: Hepatitis B Virus; NTCP: Na+- taurocholate cotransporting polypeptide. 1. Kang C, Syed YY. Bulevirtide: first approval. Drugs. 2020;80:1601-1605. 2. Alweiss L, et al. Journal of Hepatology 2024.

Bulevirtide Therapeutic Approaches



Finite treatment
To cure the infection/disease

Additional factors influencing treatment schedule:

- Phase of HBV infection (HBeAg/anti-HBe status; HBV DNA and HBsAg levels)
- IFNα contraindication, tolerability
- Patient's will and compliance to treatment

Prolonged treatment
To control the infection/disease

CSPH, clinically significant portal hypertension
EASL, J Hepatol. 2023

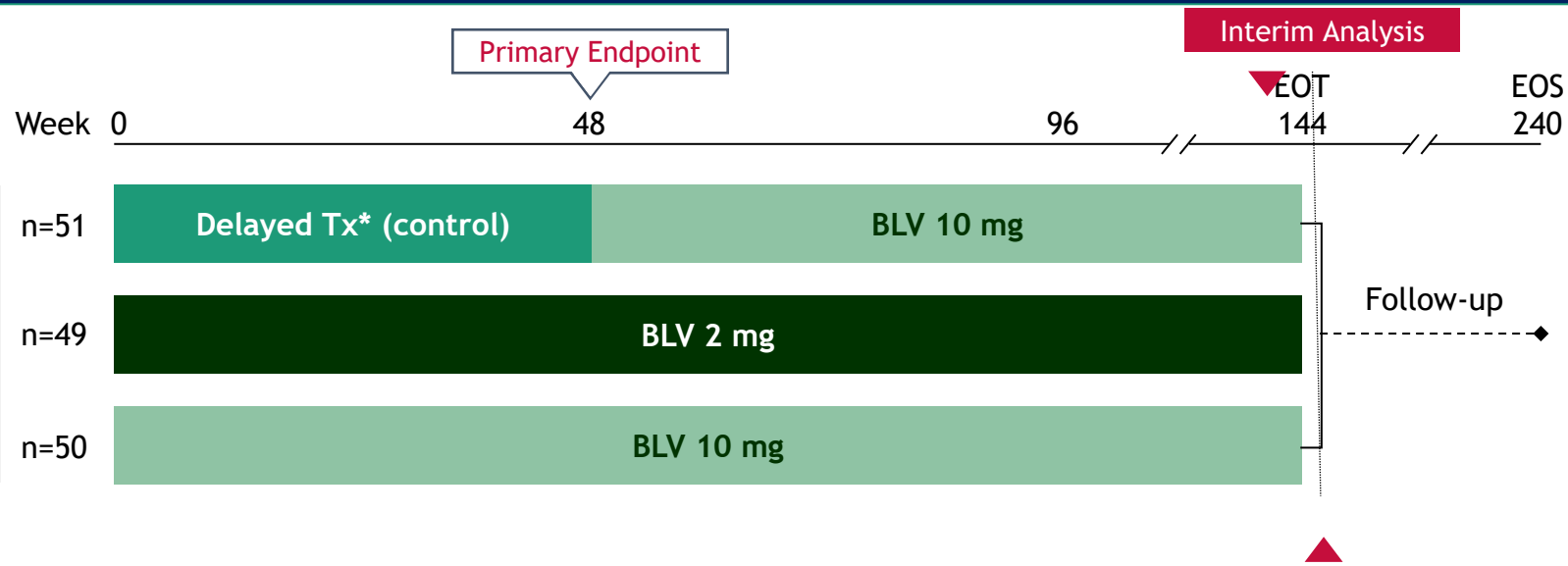
MYR301 Study Design

Multicenter, open-label, randomized, Phase 3 study

Key inclusion criteria:

- Adults with chronic hepatitis delta
- With or without compensated cirrhosis
- ALT >1× to <10× ULN, and positive serum HDV RNA

MYR301:
N=150
Randomized
1:1:1



Primary endpoint:

- Combined response at Week 48: HDV RNA undetectable** or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization

Secondary endpoints:

- Undetectable HDV RNA** at Week 48
- ALT normalization† at Week 48
- Undetectable HDV RNA** 24 and 48 weeks after EOT
- Change in liver stiffness (transient elastography) at Week 48, 96, 144, 192, and 240
- HDV RNA decrease by ≥2 $\log_{10}$ IU/mL or undetectable at Week 48

*Delayed treatment arm did not receive any BLV through Week 48; **Undetectable HDV RNA defined as <LLOQ (50 IU/mL) or target not detected; †ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites), ≤34 U/L for females and ≤49 U/L for males (all other sites). BLV, bulevirtide; EOS, end of study; EOT, end of treatment LLOQ, lower limit of quantification; Tx, treatment; ULN, upper limit of normal.

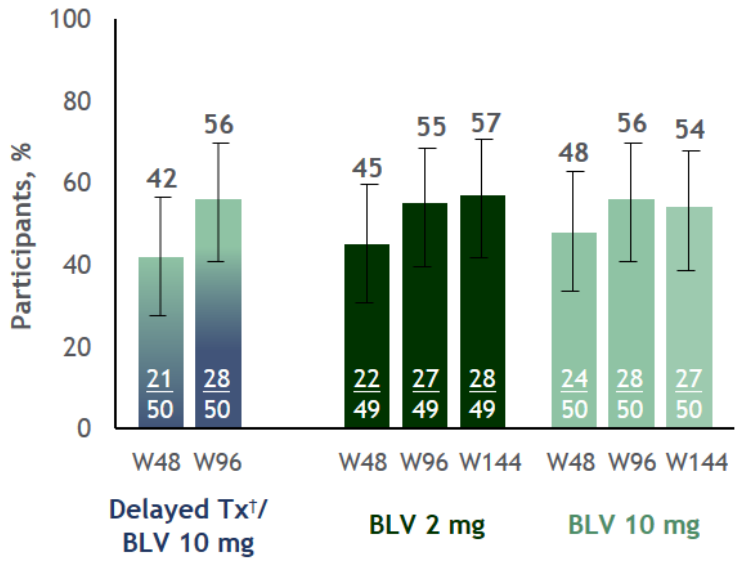
Wedemeyer H, et al. EASL 2023. Oral #OS-068; Wedemeyer H, et al. N Engl J Med 2023; 389:22-32

BLV 2 mg is the only licensed dose

MYR301: BLV Efficacy Endpoints Through Week 144

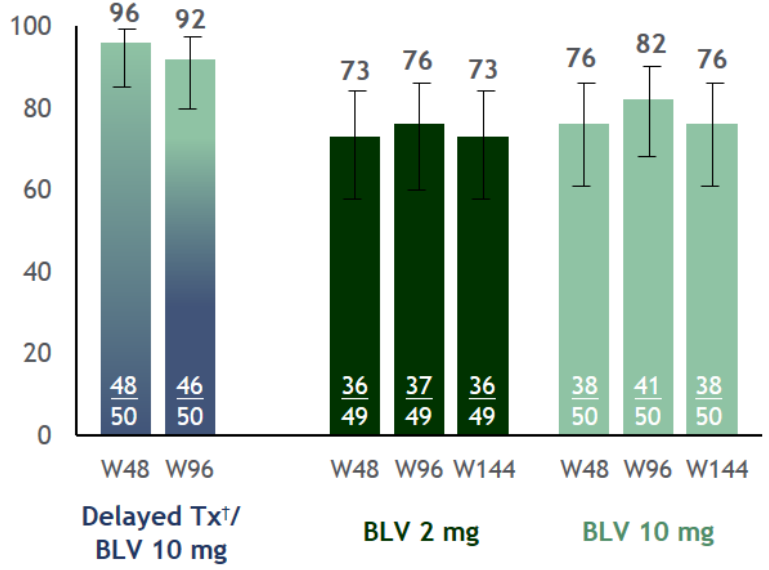
Combined Response

Undetectable HDV RNA* or ≥2 log_{10} IU/mL decline from BL and ALT normalization**



Virologic Response

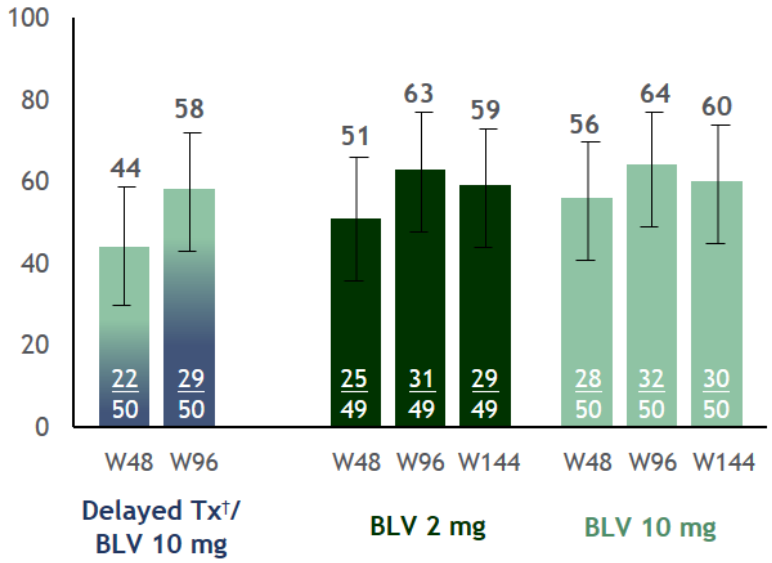
Undetectable HDV RNA* or ≥2 log_{10} IU/mL decrease from BL



Undetectable HDV RNA, %

24	52		12	20	29		20	36	50

ALT Normalization**



- Only 1 patient experienced HBsAg loss in the delayed treatment to BLV 10 mg arm

Long-term BLV therapy demonstrated improved virologic and ALT responses through 144 weeks

Lampertico P, et al. EASL 2024. Poster #LBP-029

MYR301: EOT Safety Analysis (144 weeks)

Summary of AEs

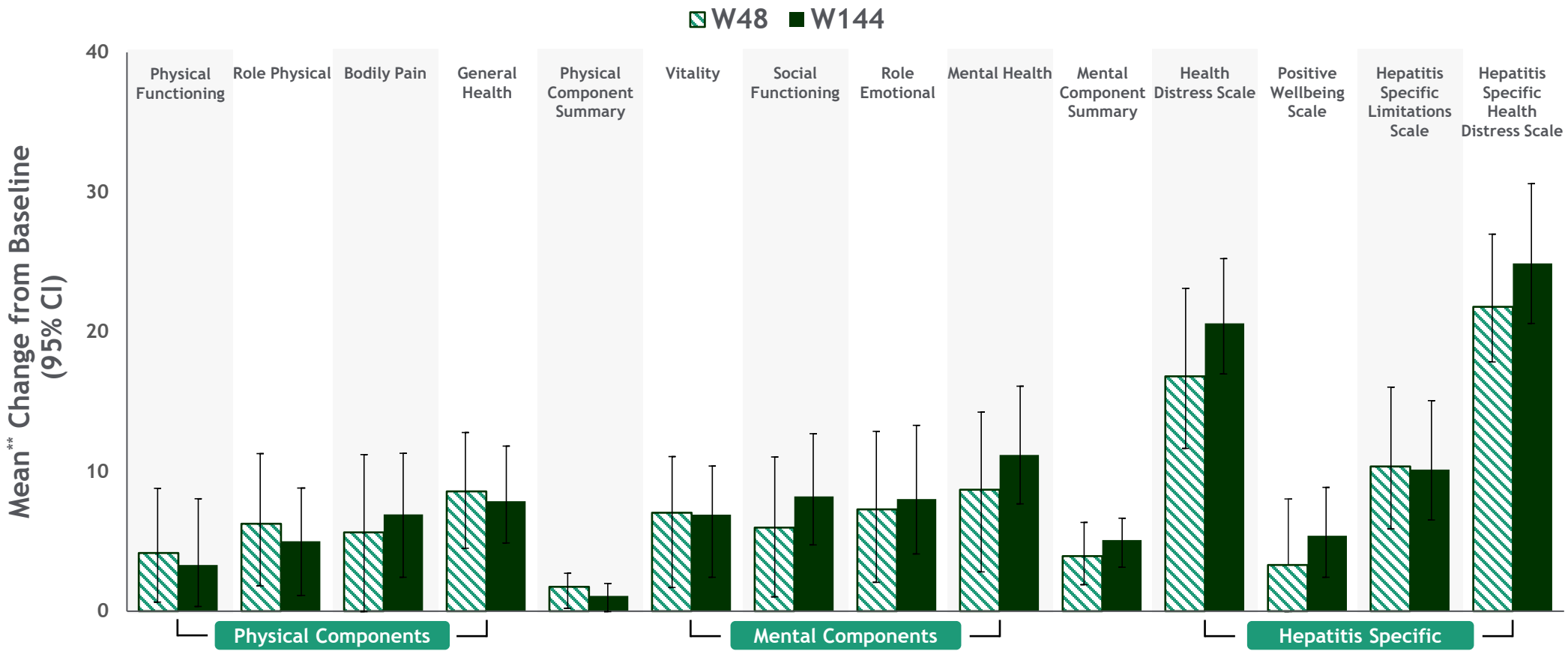
n (%)	Delayed Tx*/BLV 10 mg n=50		BLV 2 mg n=49		BLV 10 mg n=50	
	Week 48–96**	Week 48–144	Week 96	Week 144	Week 96	Week 144
Any AE	42 (84)	46 (92)	47 (96)	48 (98)	48 (96)	48 (96)
Any AE related to BLV	22 (44)	23 (46)	25 (51)	27 (55)	36 (72)	37 (74)
Any SAE	2 (4)	3 (6)	2 (4)	3 (6)	4 (8)	6 (12)
Any SAE related to BLV	0	0	0	0	0	0
AE leading to withdrawal of BLV	0	0	0	0	0	0
Grade 3–4 AE	3 (6)	5 (10)	9 (18)	12 (24)	8 (16)	10 (20)
Death†	1 (2)	1 (2)	0	0	0	0
AEs of interest‡						
Headache	7 (14)	7 (14)	9 (18)	10 (20)	12 (24)	12 (24)
Dizziness	1 (2)	1 (2)	2 (4)	2 (4)	4 (8)	4 (8)
Nausea	1 (2)	1 (2)	3 (6)	3 (6)	6 (12)	6 (12)
Pruritis	0	0	6 (12)	6 (12)	9 (18)	8 (16)
Fatigue	2 (4)	3 (6)	7 (14)	7 (14)	9 (18)	9 (18)
ISR¶	6 (12)	8 (16)	10 (20)	10 (20)	15 (30)	15 (30)

Through Week 144, there were no discontinuations, serious AEs, or deaths attributable to BLV monotherapy

Lampertico P, et al. EASL 2024. Poster #LBP-029

Patient-Reported Outcomes Through 3 Years of Treatment

Hepatitis Quality of Life Improvements from BL to W48/W144 for Patients Treated with BLV 2 mg*

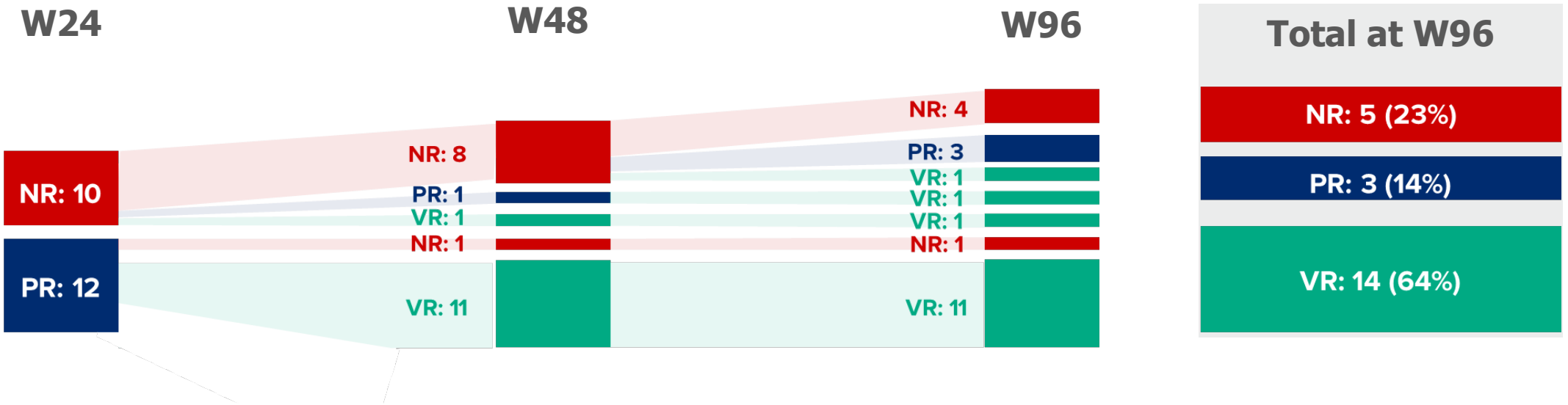


Sustained or incremental improvements of quality of life observed with BLV 2 mg long-term therapy

*n=49 at BL; by Week 144, 4 patients dropped out of the BLV 2 mg group and were excluded from analyses; **least squares mean. BL, baseline; BLV, bulevirtide; W, week.

Buti M, et al.J Hepatol 2024

BLV 2mg suboptimal responders at week 24, improve their response rates by week 96



- **92%** (11/12) of **PR** at week 24 achieve a **virologic response at week 96**
- **60%** (6/10) of **NR** at week 24 achieve **some type of response at week 96**

Only approved arms and/or the control arm are shown

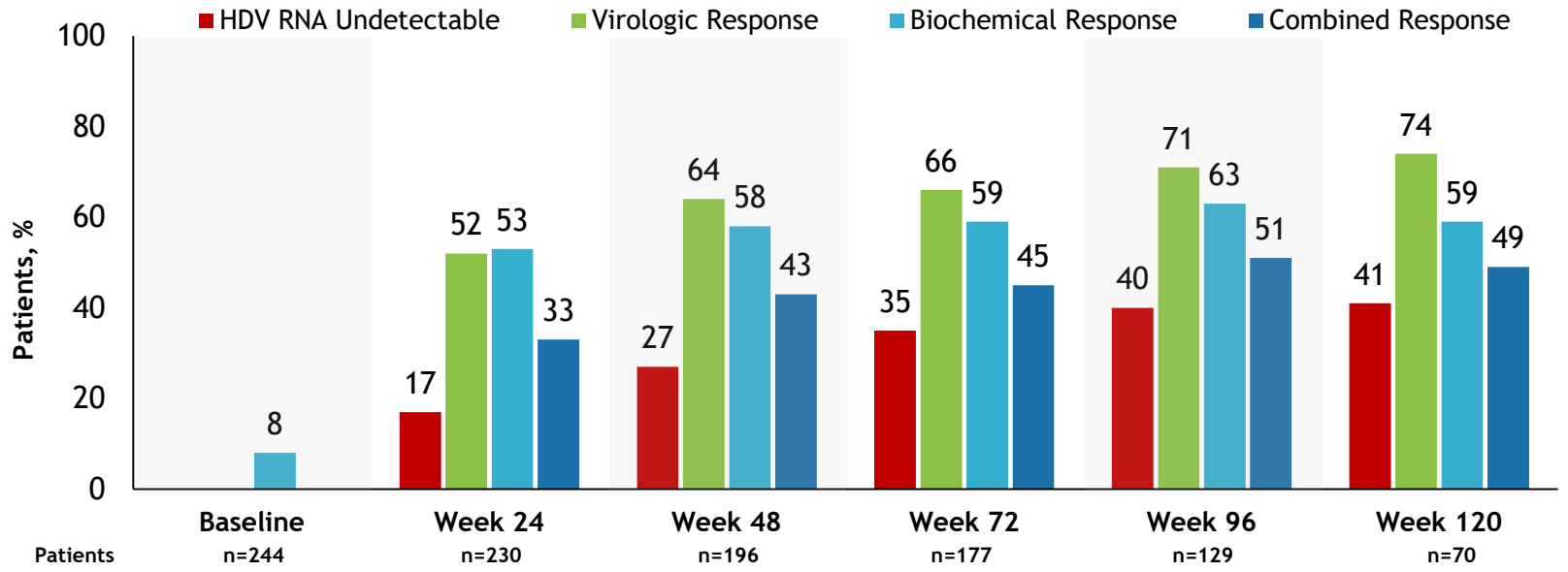
- NR: non-responder (HDV RNA decrease < 1 log10 UI/mL from BL); PR: partial responder (HDV RNA decrease ≥1 y <2 log10 UI/mL from BL); VR: virologic responder (HDV RNA decrease ≥2 log10 UI/mLfrom BL or undetectable HDV RNA). *Suboptimal response: NR o PR at W24. 1. Lampertico P, et al. AASLD: The Liver Meeting, 10-14 Novembre 2023. Presentation 63.

120 Week BLV RWD in Pan-European Cohort with Compensated Cirrhosis

Retrospective, multicenter* analysis of BLV 2 mg monotherapy in 244 patients

Baseline Characteristics	BLV 2 mg n=244
Age, median years (IQR)	49 (40–58)
Male, n (%)	148 (61)
HIV coinfection, n (%)	24 (10)
CTP score A**, n (%)	233 (95)
Esophageal varices†, n (%)	91 (54)
History of HCC, n (%)	18 (7)
Liver stiffness, median kPa (IQR)	18 (13–26)
ALT, median U/L (IQR)	80 (55–130)
Platelets, median $10^3/mm^3$ (IQR)	94 (67–145)
HDV RNA, median log_{10} IU/mL (IQR)	5.4 (4.1–6.5)
NA treatment, n (%)	224 (92)
Previous IFN treatment, n (%)	142 (58)

Effectiveness‡ of BLV Treatment Up to 120 Weeks



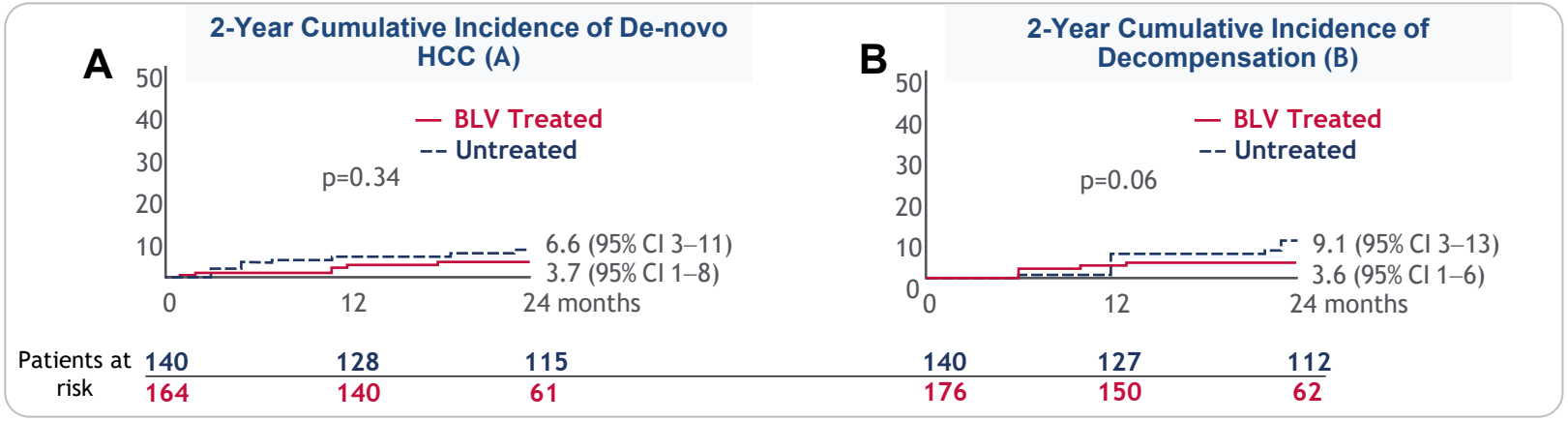
Safety

12 patients discontinued BLV treatment§ and 9 patients lost to follow-up ▪ Mild and transient pruritus in 11% of patients and ISR reported in 3% of patients ▪ 18 liver transplants and 8 deaths∫ ▪ 18 de-novo liver-related events (11 HCC, 4 ascites, 3 variceal bleeding)

BLV 2 mg in patients with advanced disease led to improvement in efficacy and remained well tolerated

*46 European centers (Italy, France, Austria, Germany, Greece, Portugal, Sweden, Switzerland, United Kingdom); **CTP A6 in 59 (24%), CTP B7 in 11 (5%); †Available in 169 (69%) of patients; ‡Virologic response: undetectable HDV RNA or ≥2 log decline from baseline; Biochemical response: ALT <40 U/L; Combined response: virologic and biochemical response; Undetectable: target not detected, <LLOQ, or <LOD); §Non-compliance n=2, virological non-response n=4, BLV-related rash n=1, liver decompensation n=2, long-term HDV RNA undetectablility n=3; ∫Liver transplants (15 for HCC, 3 for ESLD); deaths (pneumonia, intestinal infarction, non-hepatic neoplasm, HCC progression, GI bleeding, ACLF). ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; BLV, bulevirtide; CTP, Child-Turcotte-Pugh; ESLD, end-stage liver disease; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; IFN, interferon; ISR, injection site reaction; LLOQ, limit of quantification; LOD, limit of detection; NA, nucleos(t)ide analogue. Degasperi E, et al. AASLD 2024. Oral #139

In patients with cirrhosis, BLV-2 mg was associated with fewer hepatic events



Outcomes	Category	Unadjusted Cox Regression ANalysis		IPTW-Adjusted Cox Regression Analysis		IPTW-Adjusted Competing Risk Regression Model	
		HR (95% CI)	p value	HR (95% CI)	p value	SHR (95% CI)	p value
Liver-related Events	Treated vs. Untreated	0.52 (0.25-1.05)	0.07	0.38 (0.23-0.62)	**<0.0001**	0.38 (0.23-0.61)	**<0.0001**
Decompensation	Treated vs. Untreated	0.48 (0.18-1.28)	0.14	0.32 (0.16-0.63)	**0.001**	0.32 (0.17-0.61)	**0.001**
De-novo HCC	Treated vs. Untreated	0.57 (0.20-1.62)	0.29	0.50 (0.24-1.06)	0.07	0.50 (0.24-1.04)	0.06

BLV: Bulevirtide; IPTW: Inverse Probability of Treatment Weighting; HR: Hazard Ratio; SHR: Sub-distribution Hazard Ratio; CI: Confidence Interval; HCC: Hepatocellular Carcinoma 1. Degasperi S, et al. AASLD 2024. Poster #1166

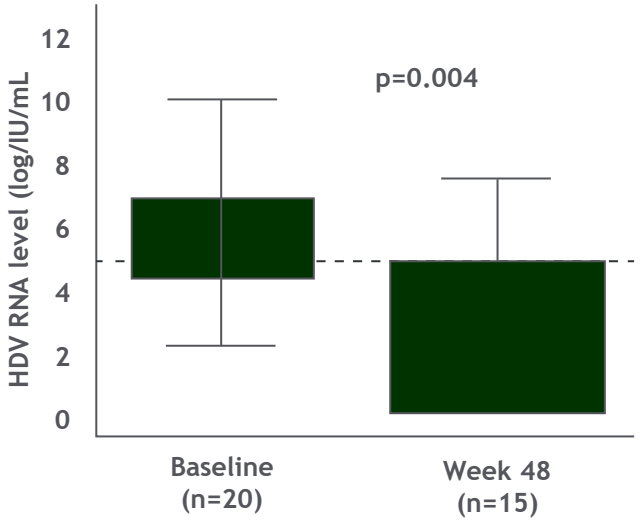
BLV in liver transplant waiting list patients

Retrospective study of BLV 2 mg in 20 patients with decompensated cirrhosis and/or HCC (January–May 2024)

Baseline Characteristics

Variable	Cohort (N=20)
Age, mean years (SD)	53 (10)
Male, n (%)	15 (75)
Ascites, n (%)	1 (5)
HCC, n (%)	8 (40)
LSM, mean kPa (range)	24 (10–58)
CTP Score	
A, n (%)	14 (70)
B, n (%)	1 (5)
C, n (%)	5 (25)
Platelets, mean 10^3/mmolL (range)	94 (50–286)
ALT, mean U/L (range)	91 (60–136)
HDV RNA, mean $\log_{10}$ IU/mL (range)	6 (2–10)

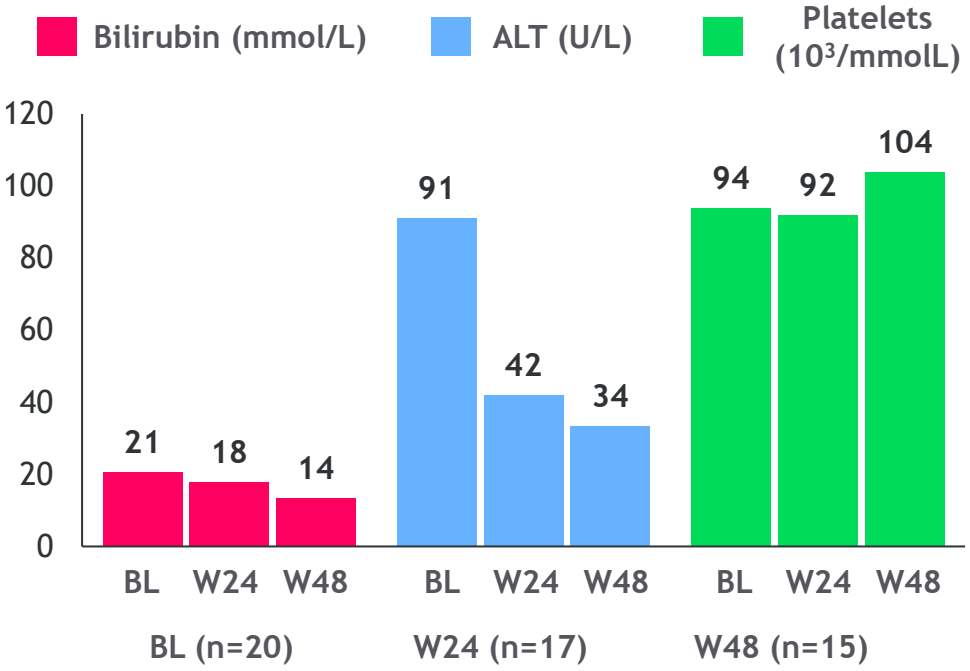
W48 HDV RNA Levels



Improvement in Hepatic Function in HCC patients (n=8):

- **12.5%** HCC downstaging
- **62.5%** clearance for locoregional therapy

Biochemical Parameters During BLV Therapy



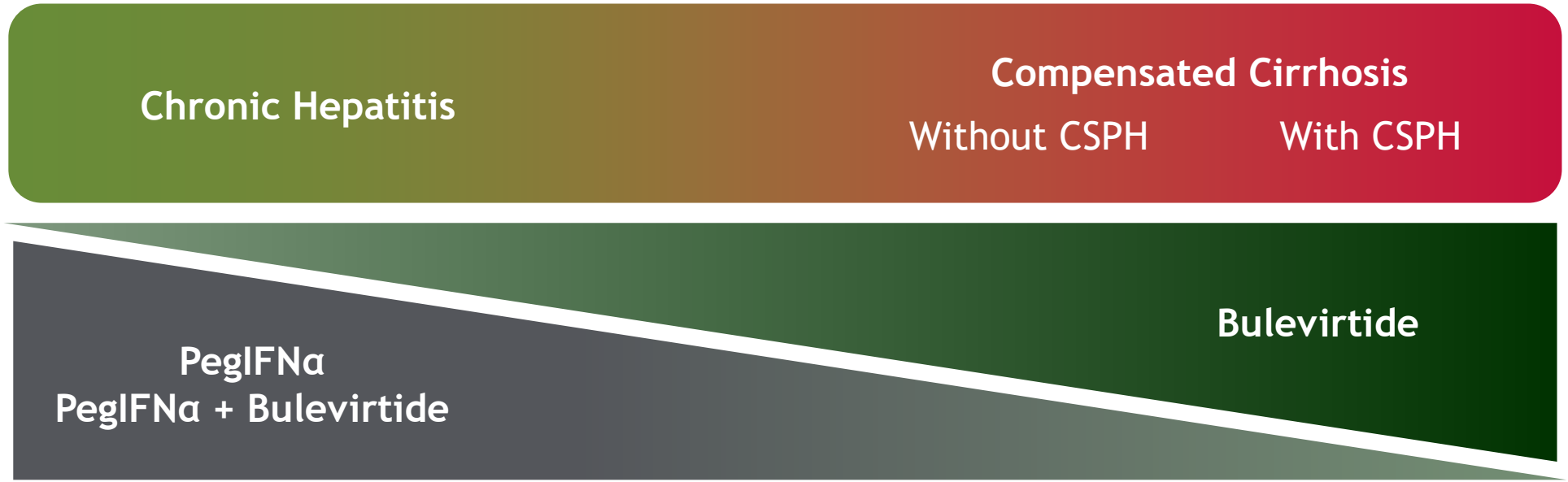
Safety: No treatment-related serious AEs

BLV for 48 weeks demonstrated improved hepatic function in patients on LT waiting list

Meszaros M, et al. Liver International 2025

‡

Therapeutic Approaches



Finite treatment
To cure the infection/disease

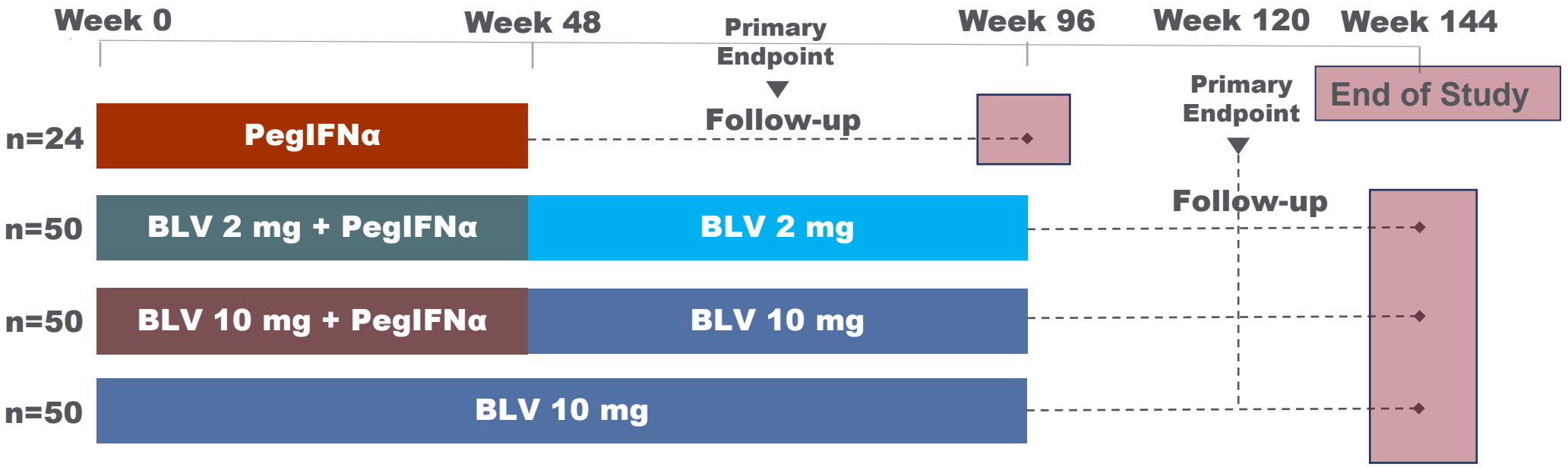
Additional factors influencing treatment schedule:

- Phase of HBV infection (HBeAg/anti-HBe status; HBV DNA and HBsAg levels)
- IFNα contraindication, tolerability
- Patient's will and compliance to treatment

Prolonged treatment
To control the infection/disease

CSPH, clinically significant portal hypertension
EASL, J Hepatol. 2023

BLV Combination therapy. Study Design



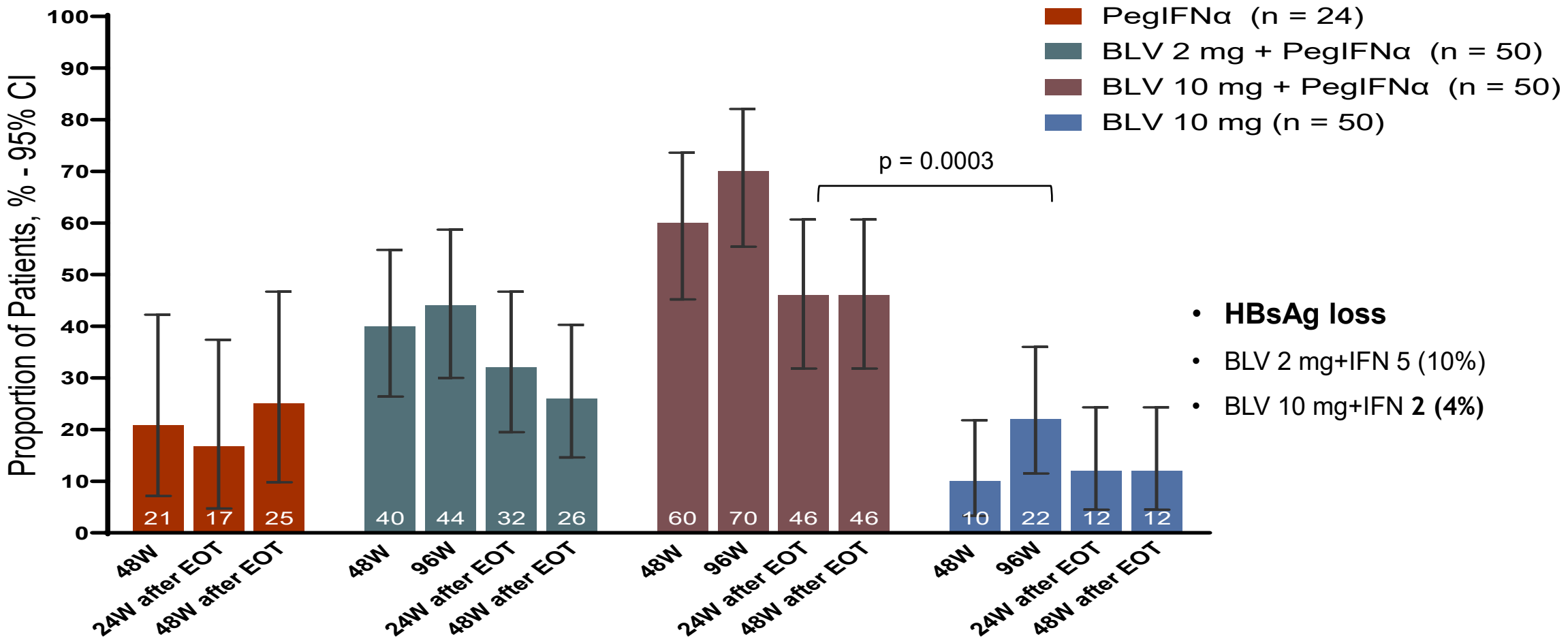
- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

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.

Undetectable HDV RNA at 48 Week after EOT

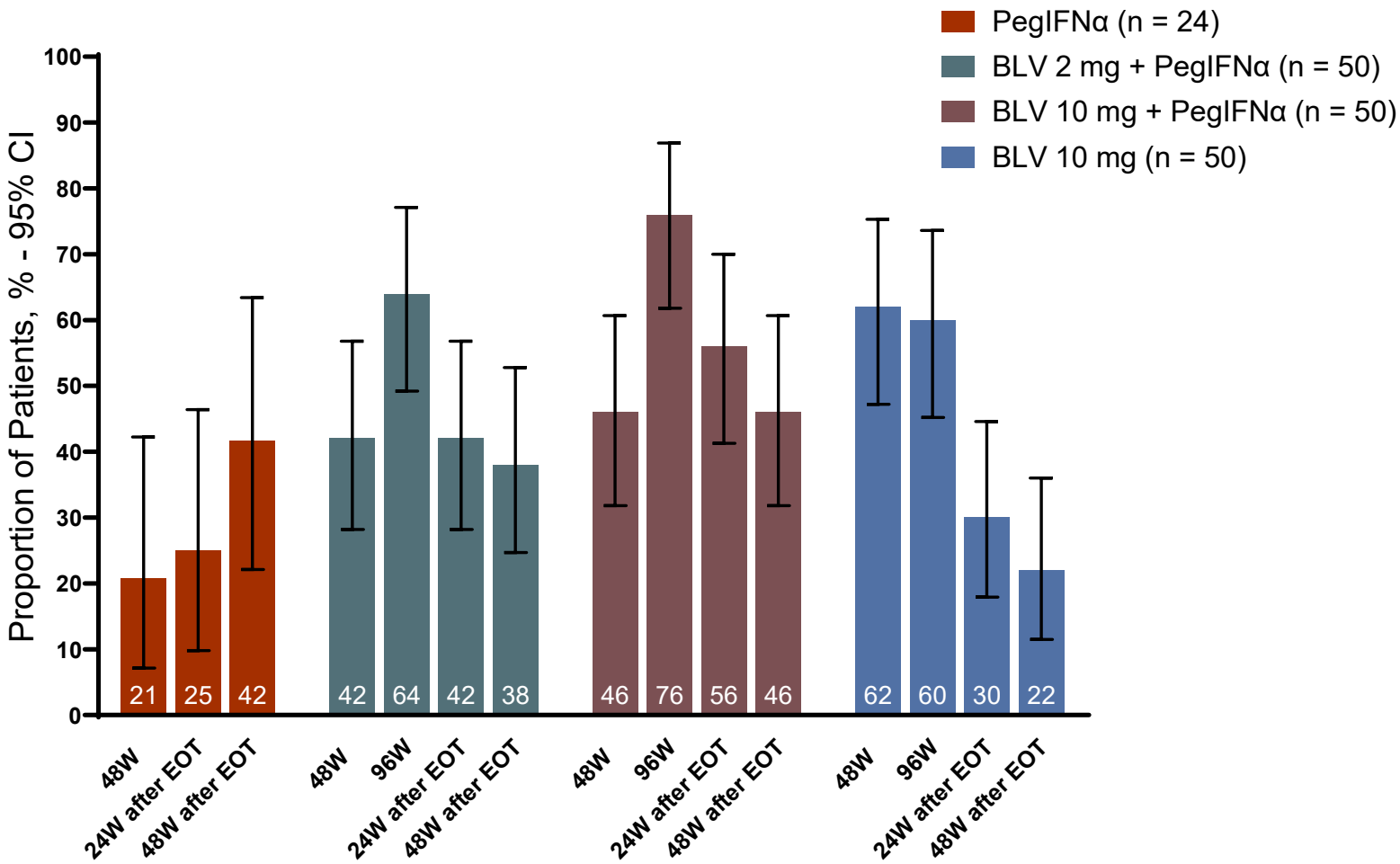


- **HBsAg loss**
- BLV 2 mg+IFN 5 (10%)
- BLV 10 mg+IFN **2 (4%)**

- 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

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.

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

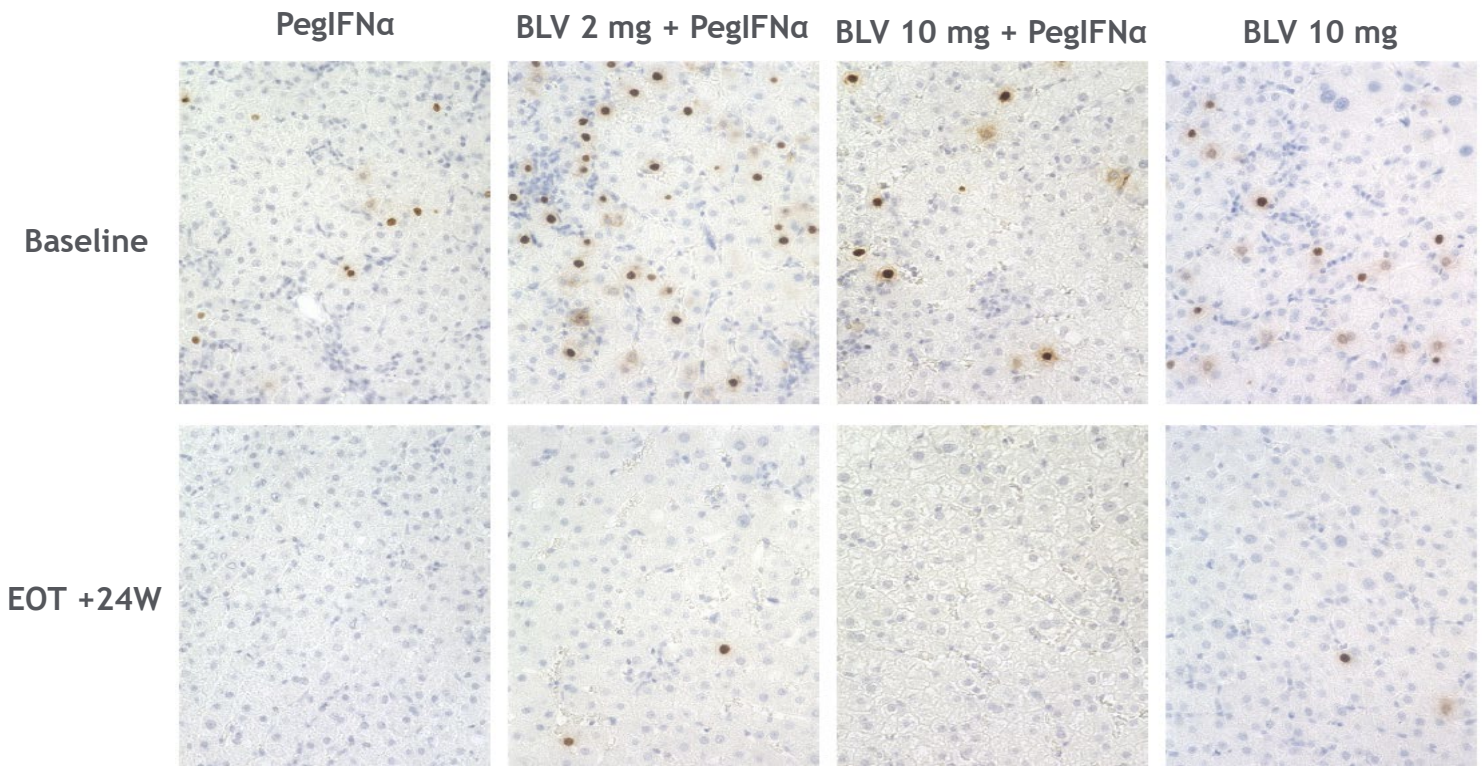
- Safety profile observed with BLV and PegIFNα was consistent with the known safety profile of each drug
- Few Grade 3 TEAEs related to BLV, no SAE related to BLV

[#]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.

Intrahepatic Analysis of BLV + PegIFNα

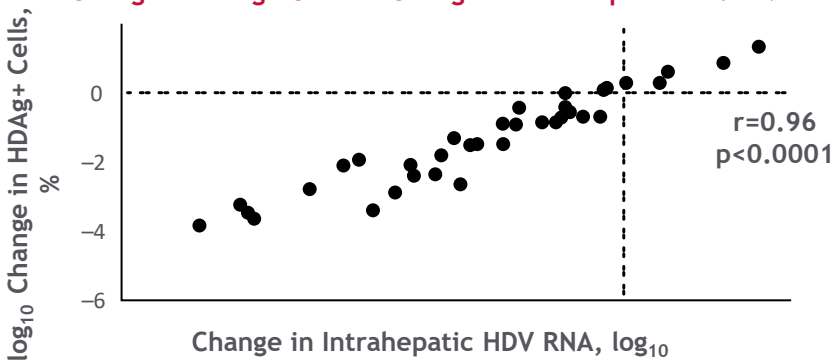
Histological analysis of paired biopsies treated with BLV ± PegIFNα (N=51)

Change in HDAg+ Cells (n=44)

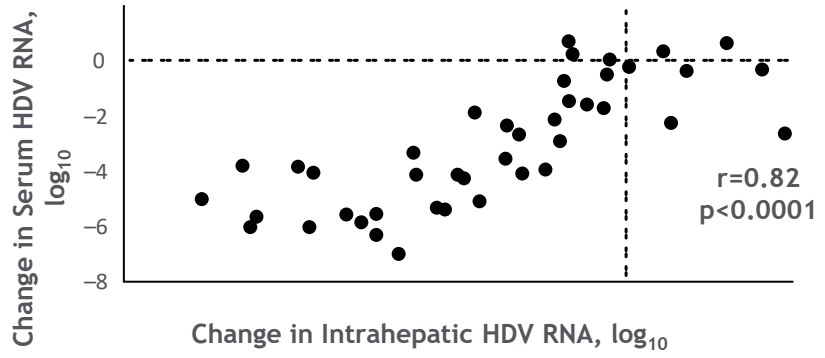


Correlation Analyses From BL to EOT +24W

Change in HDAg+ Cells vs Change in Intrahepatic HDV RNA



Change in Serum HDV RNA vs Change in Intrahepatic HDV RNA



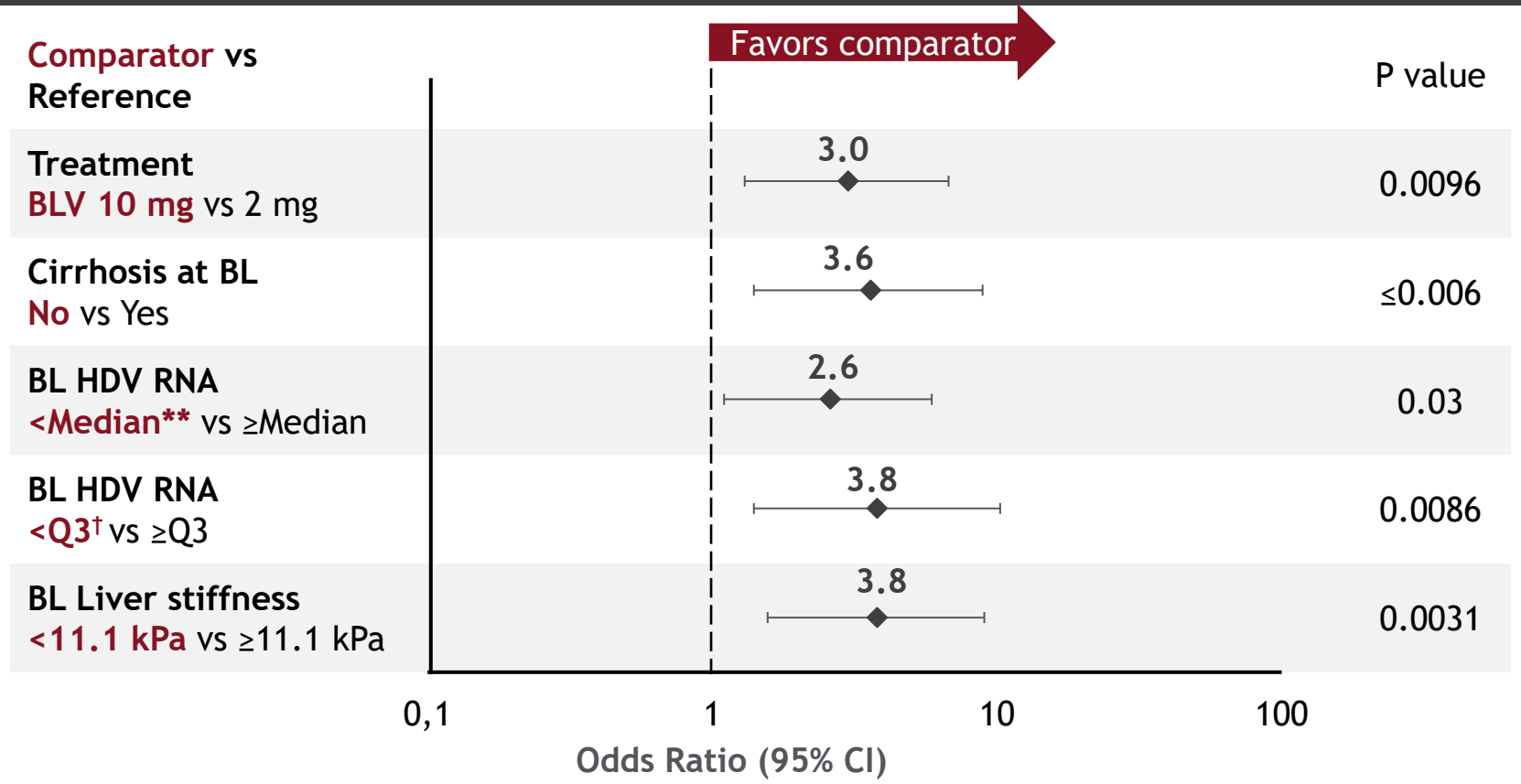
Intrahepatic and serum HDV RNA reductions are strongly correlated and reflect a reduction of infected cells

BL, baseline; BLV, bulevirtide; EOT, end of treatment; HDAg, hepatitis D antigen; PegIFNα, pegylated interferon alpha; W, week.

Allweiss L, et al. EASL 2024. Oral #OS-122

Predictors of Undetectable HDV RNA at EOT

Baseline Predictors of Undetectable HDV RNA* at EOT With BLV (2 mg or 10 mg) + PegIFNα (n=100)



HDV RNA undetectability at EOT is driven by treatment with BLV 10 mg and BL absence of cirrhosis, lower liver stiffness, and lower HDV RNA

*HDV undetectability was defined as <LLOQ, TND via ultra-sensitive HDV PCR (RoboGene® 2.0, Kobos Green Diagnostics; LLOQ=50 IU/mL; LOD=8 IU/mL). †Median=5.54 log_{10} IU/mL; Q1=5.19 log_{10} IU/mL. BL, baseline; BLV, bulevirtide; CI, confidence interval; EOT, end of treatment; LLOQ, lower limit of quantificaiton; LOD, limit of detection; PegIFNα, pegylated interferon alpha; TND, target not detected, Q3, third quartile.

Zoulim F, et al. EASL 2024. Poster #FRI-371

Summary

- **Bulevirtide monotherapy** is the **first** and **unique approved treatment** for Chronic Hepatitis Delta in patients with compensated liver disease
  - BLV **2 mg/day** has shown **57%** of **combined response, 73%** of **virologic response** and **59%** of **ALT normalization after 144 weeks**
  - **It is well tolerated,** without relevant adverse events
  - Preliminary results of BLV in patients with cirrhosis, was associated with fewer hepatic events
  - The optimal duration of BLV treatment is not yet defined. Until more data are available, long-term treatment may be considered

Summary

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

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 48 week after EOT

Limitation side effects and contraindications of IFN