

Current therapeutic approaches for chronic hepatitis D

Maria Buti, MD Barcelona, Spain



Disclosure of Conflicts of Interest

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

Hepatitis D

- Hepatitis delta virus (HDV) is a satellite virus, requires the envelope protein
from hepatitis B virus (HBV) to infect hepatocytes¹
- Between 10-20 million people are infected with HDV worldwide²
- 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}

Therapeutic Approaches for HDV therapy

Past

PegIFN

Currently

Bulevirtide (BLV)

BLV+PegIFN

Future

PegIFN is not a friendly drug

- Antiviral and Immunemodulator
- Subcutaneous 180 mcg/weekly for 48 weeks
- IFN Contraindications
- Side effects typical of IFN
- Undetectable viremia 20-25% at the end of treatment
- Early and Late relapse



Therapeutic Approaches for HDV therapy

Past

PegIFN

Currently

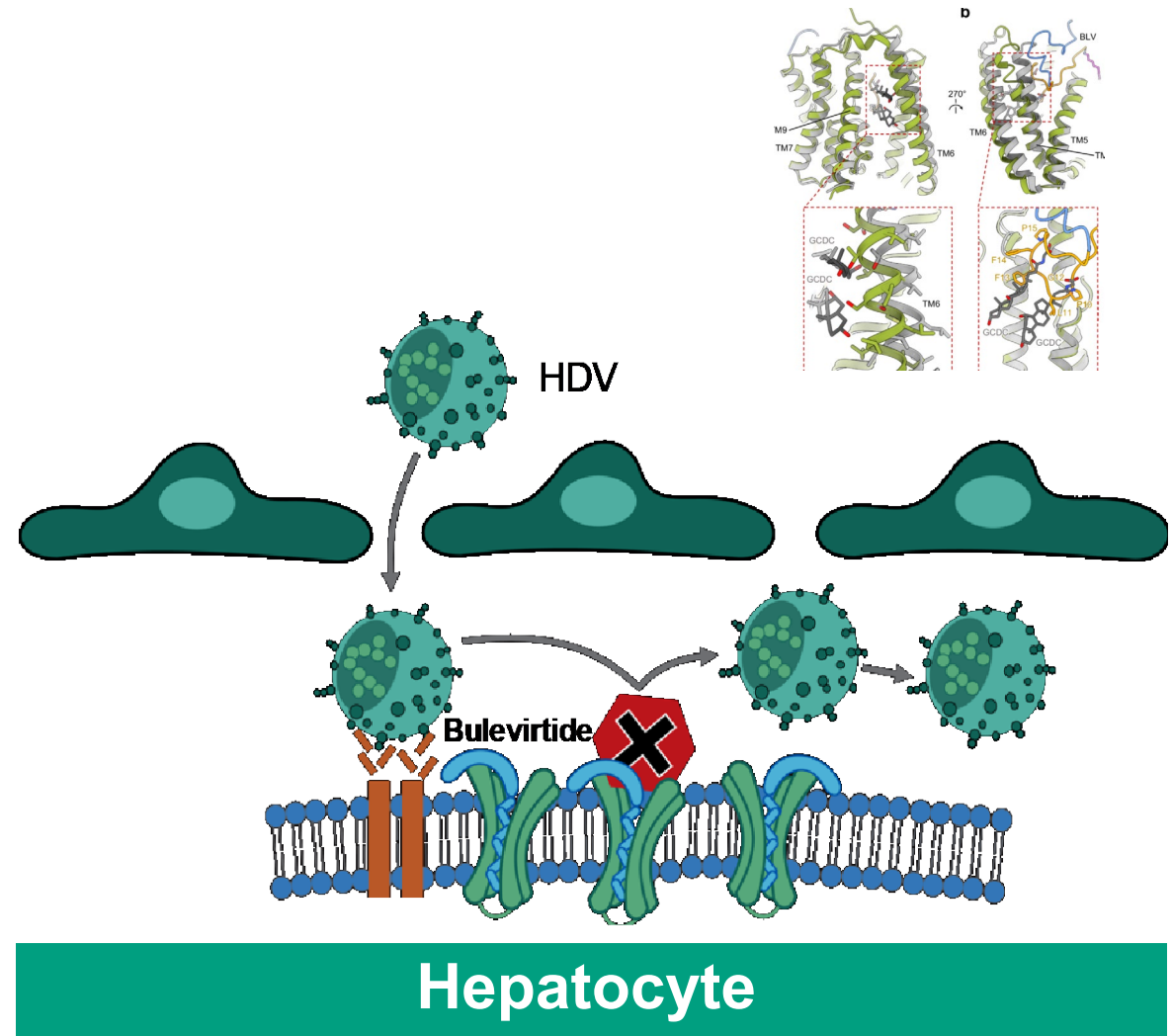
Bulevirtide (BLV)

BLV+PegIFN

Future

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
- The mechanism of action increases bile acids (NTCP is also a bile acid receptor)
- Bulevirtide is not an antiviral, it doesn't act directly by inhibiting HDV replication in infected cells
- Subcutaneous injection daily³



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

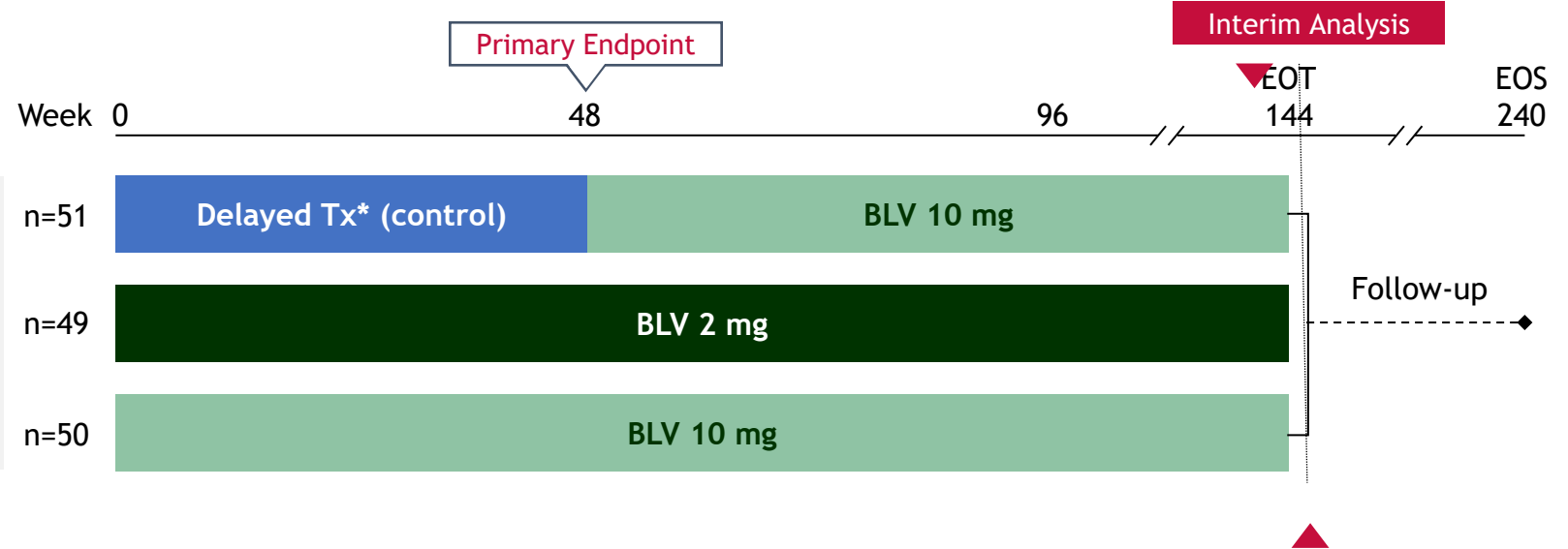
MYR301 Study Design

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 $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalization

Secondary endpoints:

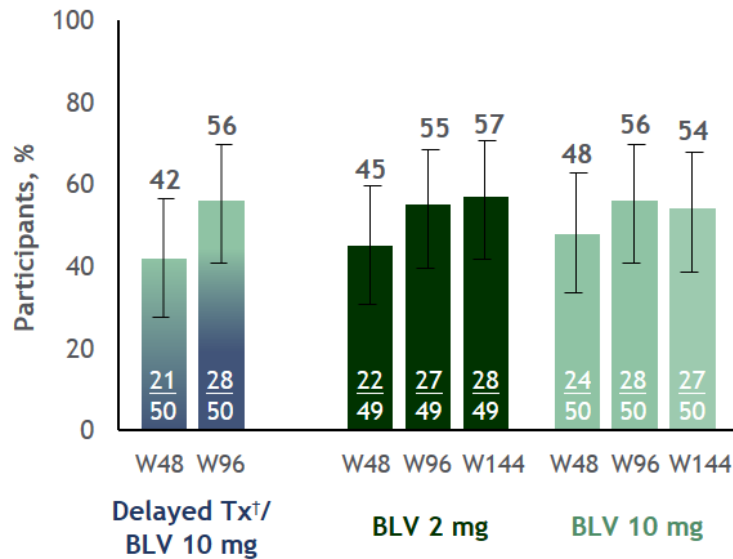
- Undetectable HDV RNA** at Week 48
- ALT normalization[†] at Week 48
- Undetectable HDV RNA** 24 and 48 weeks after EOT
- Change in liver stiffness (transient elastography) at Week 48, 96, 144, 192, and 240
- HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL or undetectable at Week 48

*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.

MYR301: BLV Efficacy Endpoints Through Week 144

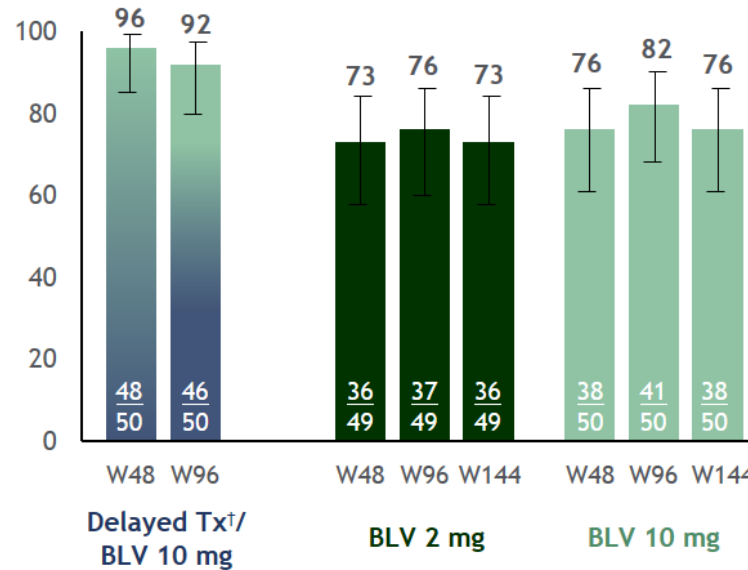
Combined Response

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

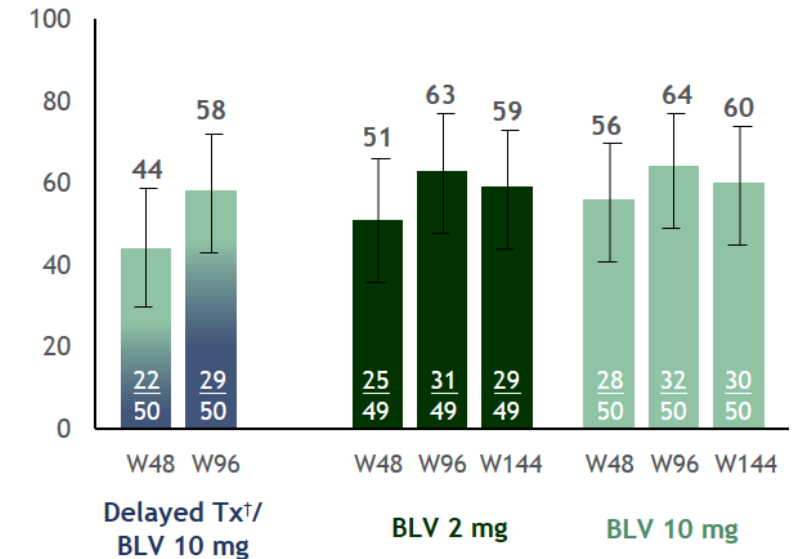


Virologic Response

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



ALT Normalization**



Undetectable HDV RNA, %

24 52 12 20 29 20 36 50

- 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

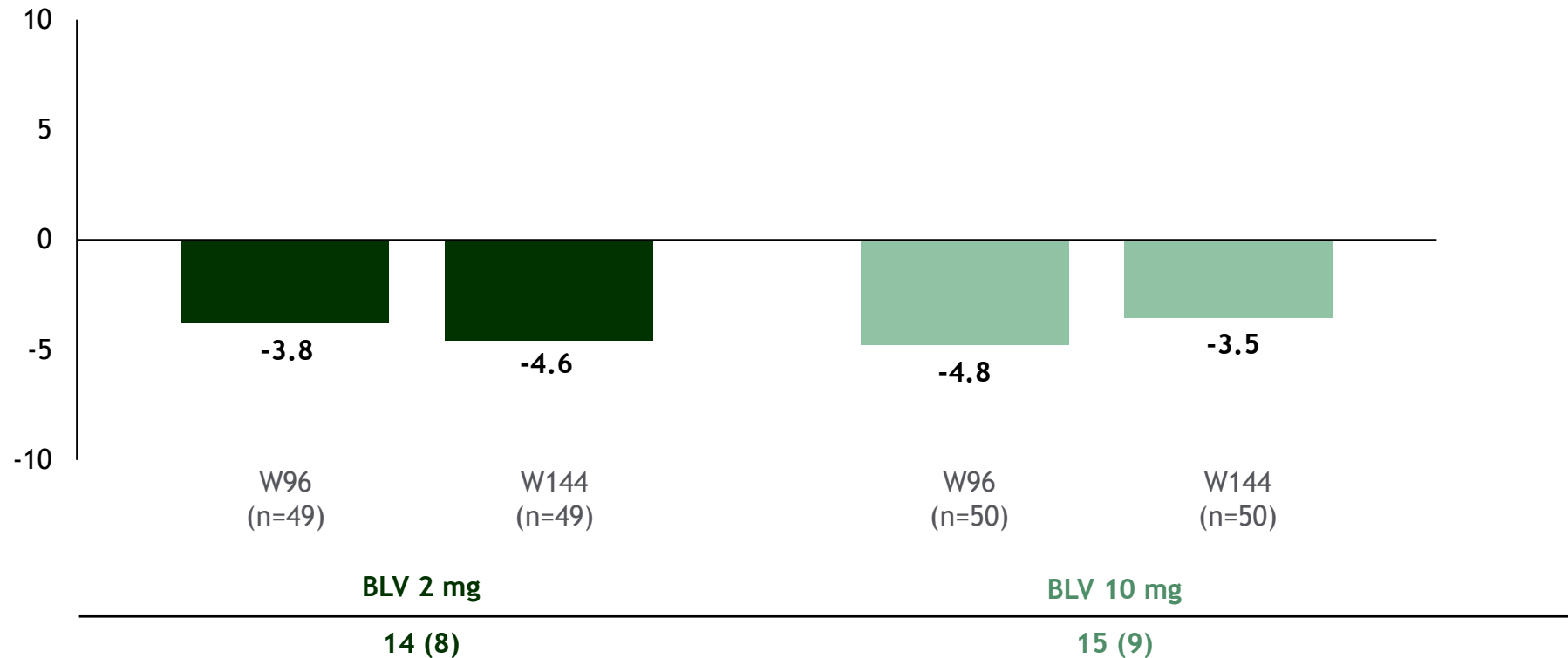
MYR301: EOT Safety Analysis (144 weeks)

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

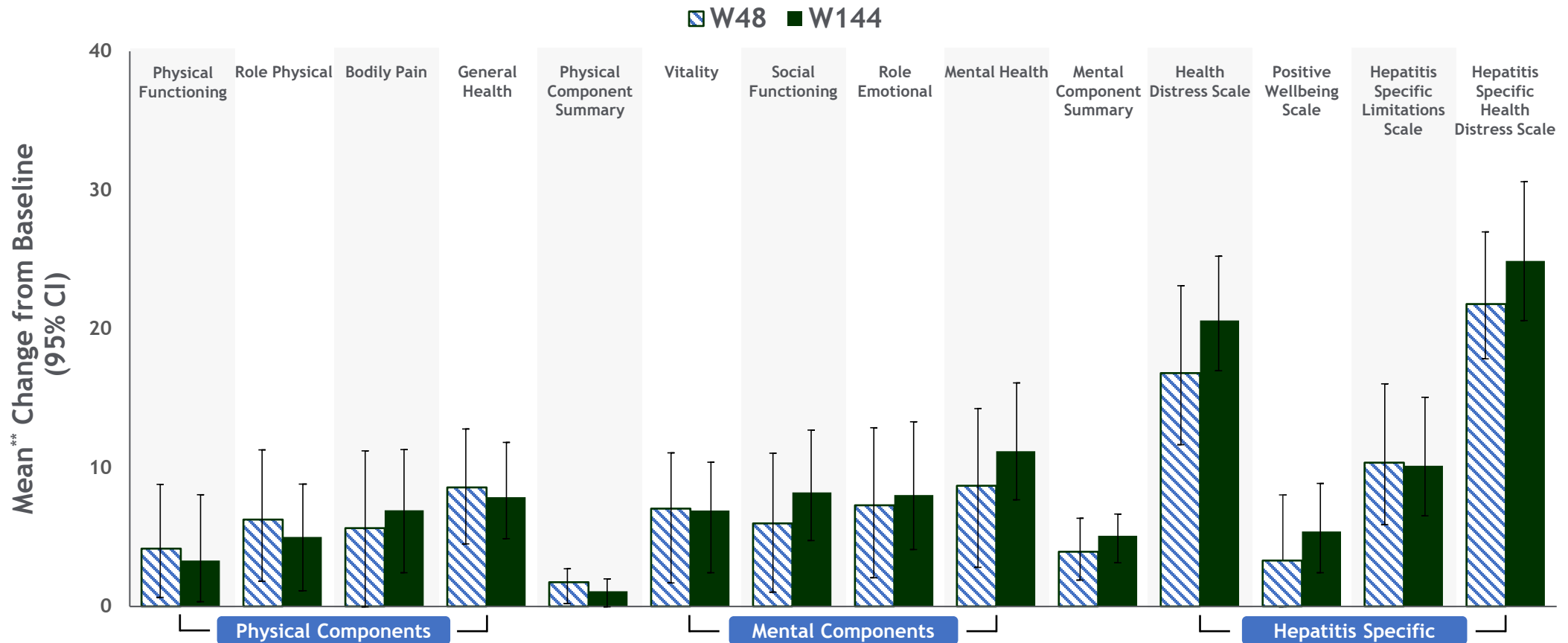
MYR301: Changes in liver stiffness



Liver stiffness measured by elastography remained stable or improved over 144 weeks of BLV monotherapy

Patient-Reported Outcomes Through 3 Years of Treatment

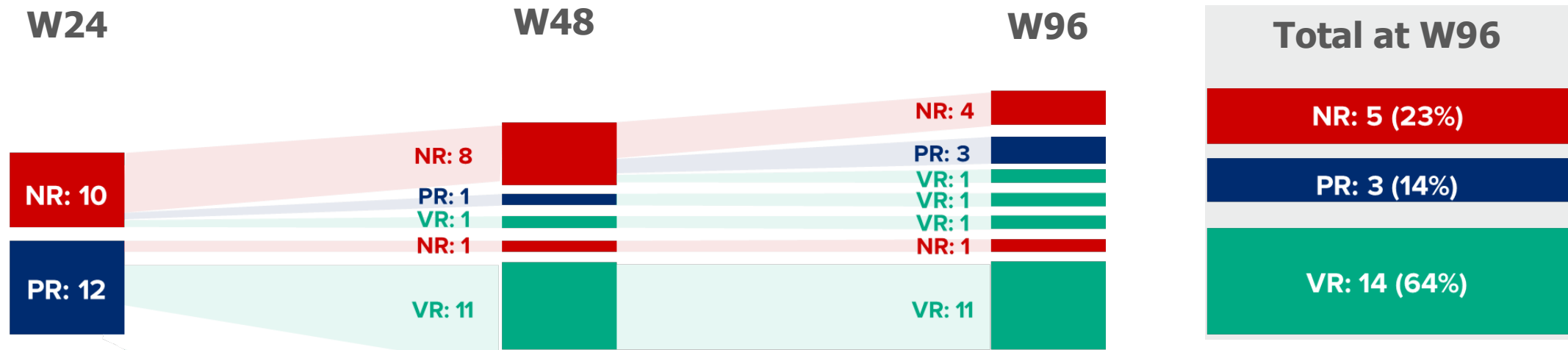
Hepatitis Quality of Life Improvements from BL to W48/W144 for Patients Treated with BLV 2 mg*



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.

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

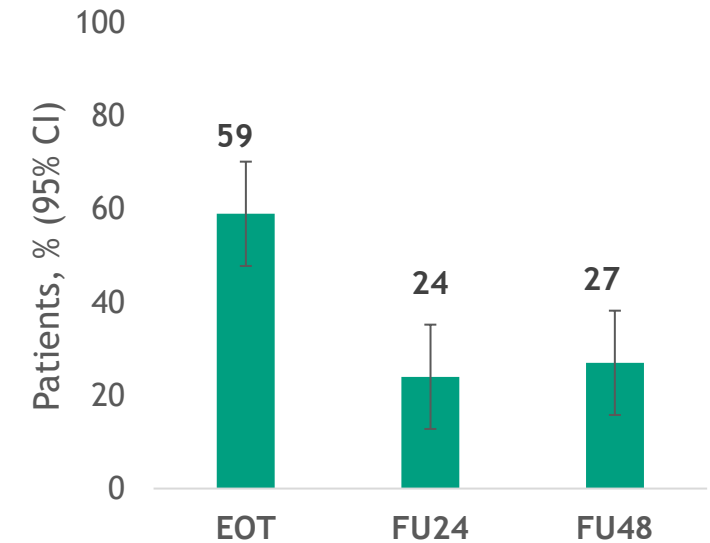
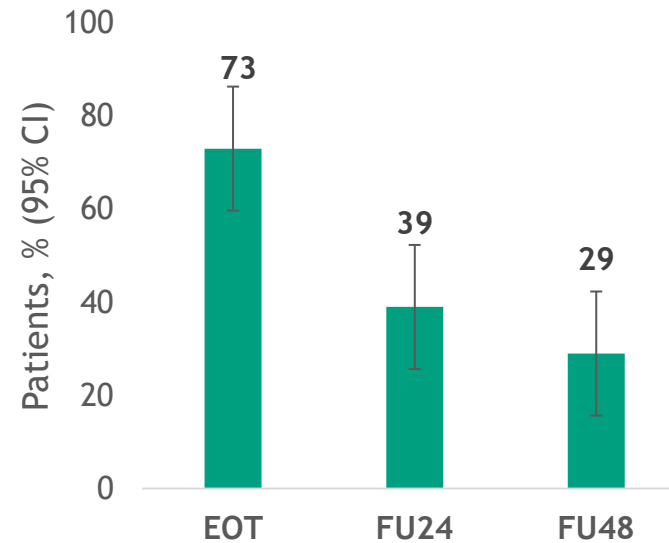
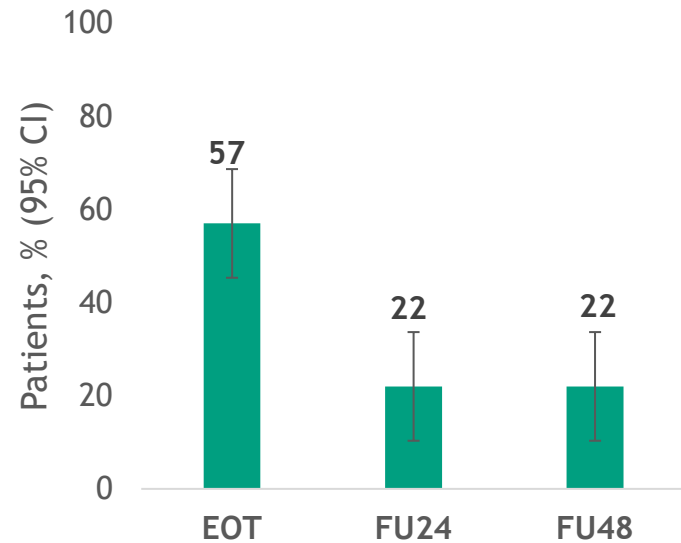
• NR: non-responder (HDV RNA decrease < 1 log₁₀ UI/mL from BL); PR: partial responder (HDV RNA decrease ≥1 y <2 log₁₀ UI/mL from BL); VR: virologic responder (HDV RNA decrease ≥2 log₁₀ UI/mL from BL or undetectable HDV RNA). *Suboptimal response: NR or PR at W24. 1. Lampertico P, et al. AASLD: The Liver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

After 48 weeks of follow-up with Bulevirtide 2 mg, patients experienced a decrease in response rates and undetectable RNA levels

Combined response
Undetectable HDV RNA or ≥ 2 log₁₀ IU/mL decline from baseline and ALT normalisation[†]

Virologic response
Undetectable* HDV RNA or ≥ 2 log₁₀ IU/mL decline from baseline

ALT[†] normalisation



% Undetectable HDV RNA* **29** **18** **16**

1 out of every 2 patients who were undetectable after 144 weeks with Bulevirtide 2mg, remained undetectable after 48 weeks of follow-up

Only arm with the approved dose and/or the control arm are shown

Patients with missing values were considered non responders; 95% CIs were calculated based on the Clopper-Pearson exact method. [†]ALT normalisation was defined at Russian sites as ≤ 31 U/L for females and ≤ 41 U/L for males, and at all other sites as ≤ 34 U/L for females and ≤ 49 U/L for males. *Undetectable HDV RNA was defined as $< \text{LLOQ}$ (50 IU/mL; target not detected). ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); HDV, hepatitis delta virus. 1. Aleman S. et al. Efficacy and Safety of Bulevirtide Monotherapy for Chronic Hepatitis Delta: Posttreatment Results Through 48 Weeks After the End of Treatment From an Interim Analysis of a Randomized Phase 3 Study, MYR301. AASLD: The Liver Meeting. 15-19 Novembre 2024. Poster 1147.

After treatment discontinuation, ALT elevations were observed

	BLV 2 mg	
Patients, n (%)	EOT (n = 49)	EOT to FU48 (n = 46)
Any AE	48 (98)	31 (67)
Any AE related to BLV	27 (55)	N/A
Any Grade 3 or 4 AE	12 (24)	6 (13)
Any SAE	3 (6)	3 (7)
Any AE leading to withdrawal of BLV	0	N/A
Death	0	0
Hepatic AEs	14 (29)	21 (46)
Hepatic SAEs	0	3 (7)

Post-treatment safety (FU48):

- 34% (47/140) of patients had ALT > 5x ULN*
- 10% (14/140) of patients had ALT > 10x ULN#
- 15 patients restarted BLV in the posttreatment period up to FU48, 10 of whom had posttreatment ALT > 5 × ULN

Only arm with the approved dose and/or the control arm are shown

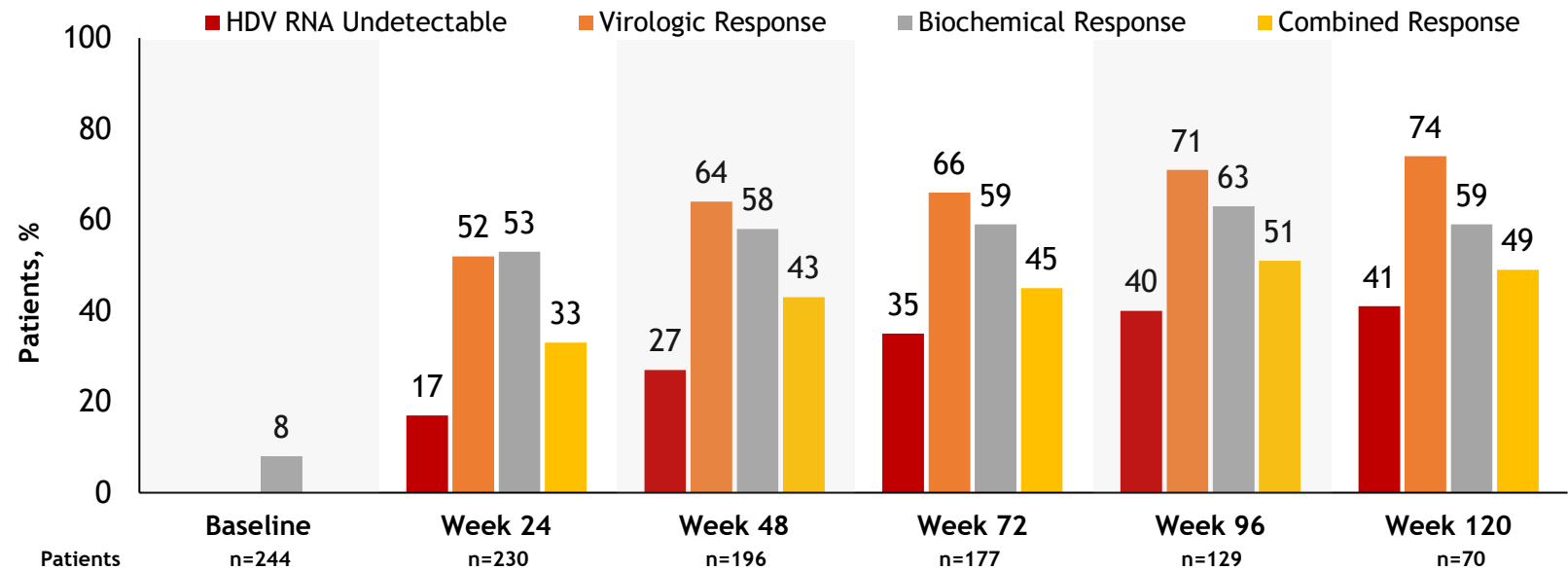
*The denominator for the percentage calculation was the number of patients in the treatment group with ≥ 1 ALT value after the last BLV dose. #Includes SAE report data (2 participants) reported by the principal investigator using local labs. Two BLV restarts reported in SAE reports only; EOT: end of treatment; FU: follow-up; N/A: no applicable; ULN: upper limit of normality. 1. Aleman S. et al. Efficacy and Safety of Bulevirtide Monotherapy for Chronic Hepatitis Delta: Posttreatment Results Through 48 Weeks After the End of Treatment From an Interim Analysis of a Randomized Phase 3 Study, MYR301. AASLD: The Liver Meeting. 15-19 Novembre 2024. Poster 1147.

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



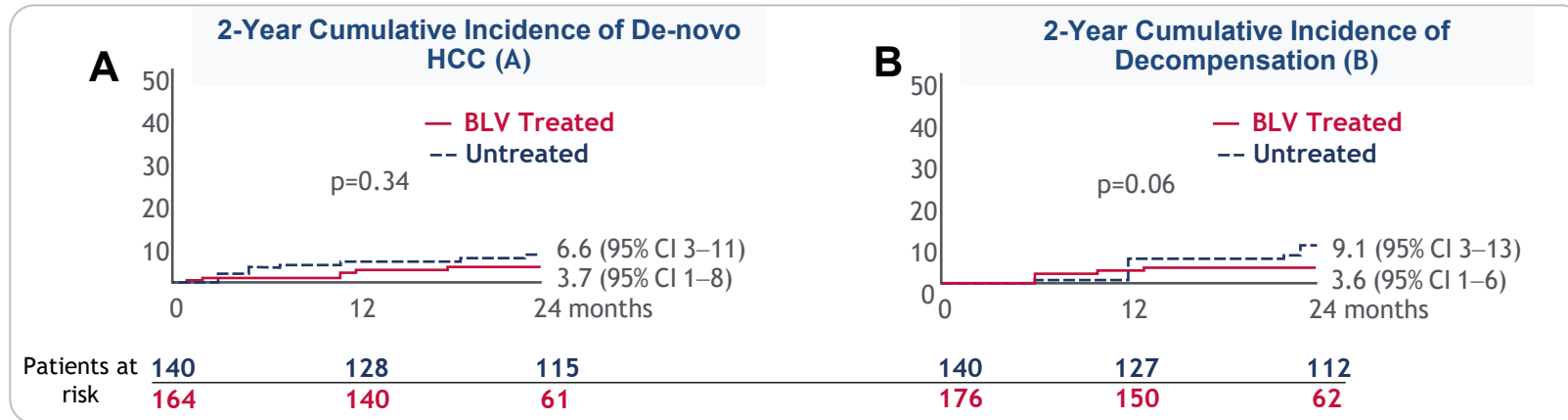
Safety

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 undetectability 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. Degasper 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

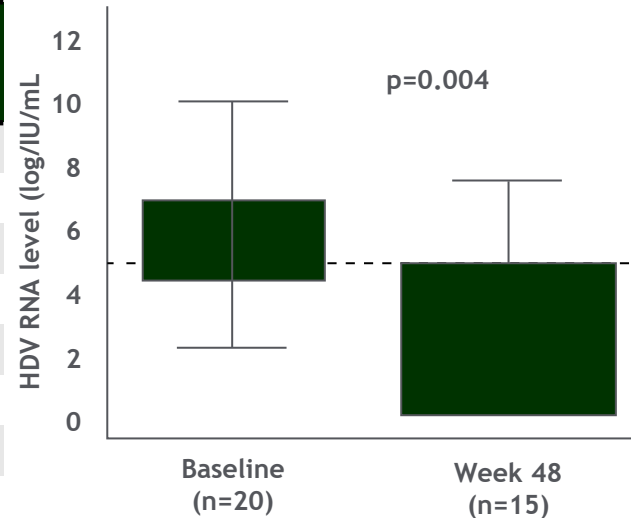
BLV in liver transplant waiting list patients

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)

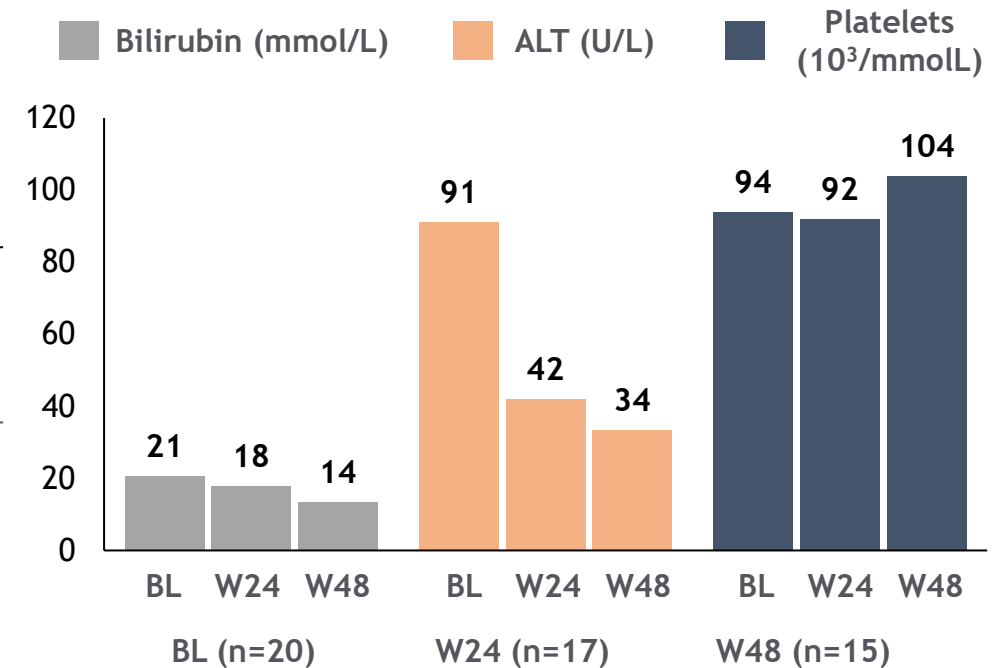
W48 HDV RNA Levels



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

Summary Bulevirtide monotherapy

- **First and unique approved treatment for compensated Chronic Hepatitis D**
- **BLV 2 mg 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**
- **BLV in patients with cirrhosis, was associated with fewer hepatic events**
- **Discontinuing BLV is associated with virological and biochemical relapses**
- **The optimal duration of BLV treatment is not yet defined. Until more data are available, long-term treatment may be considered**

Therapeutic Approaches for HDV therapy

Past

PegIFN

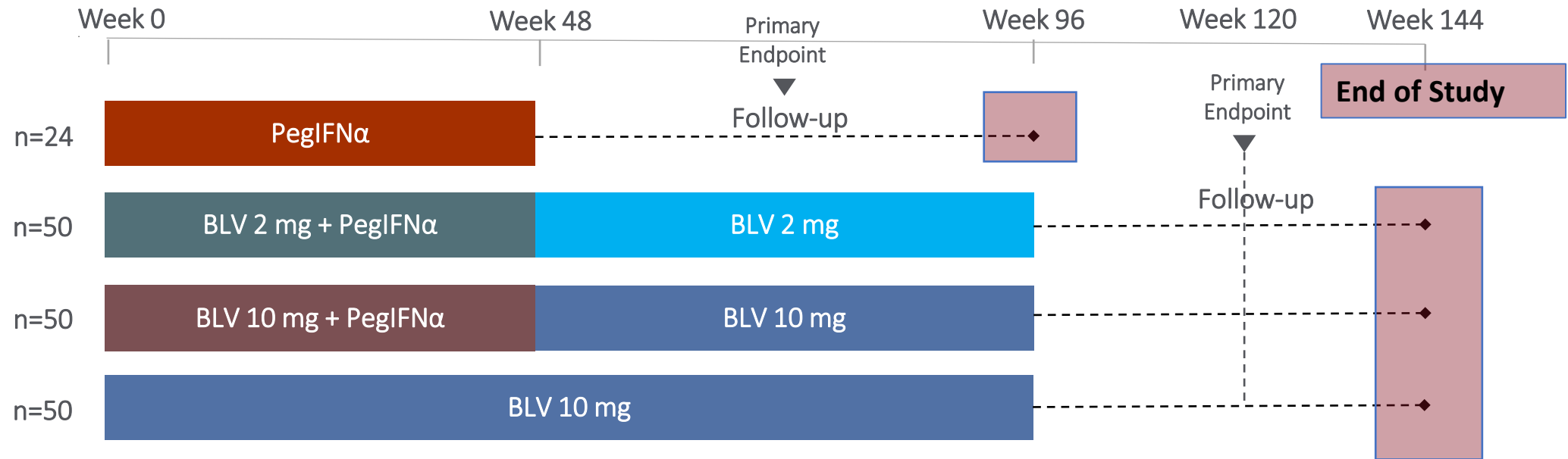
Currently

Bulevirtide (BLV)

BLV+PegIFN

Future

Phase II study BLV±PegIFN vs.PegIFN for CHD

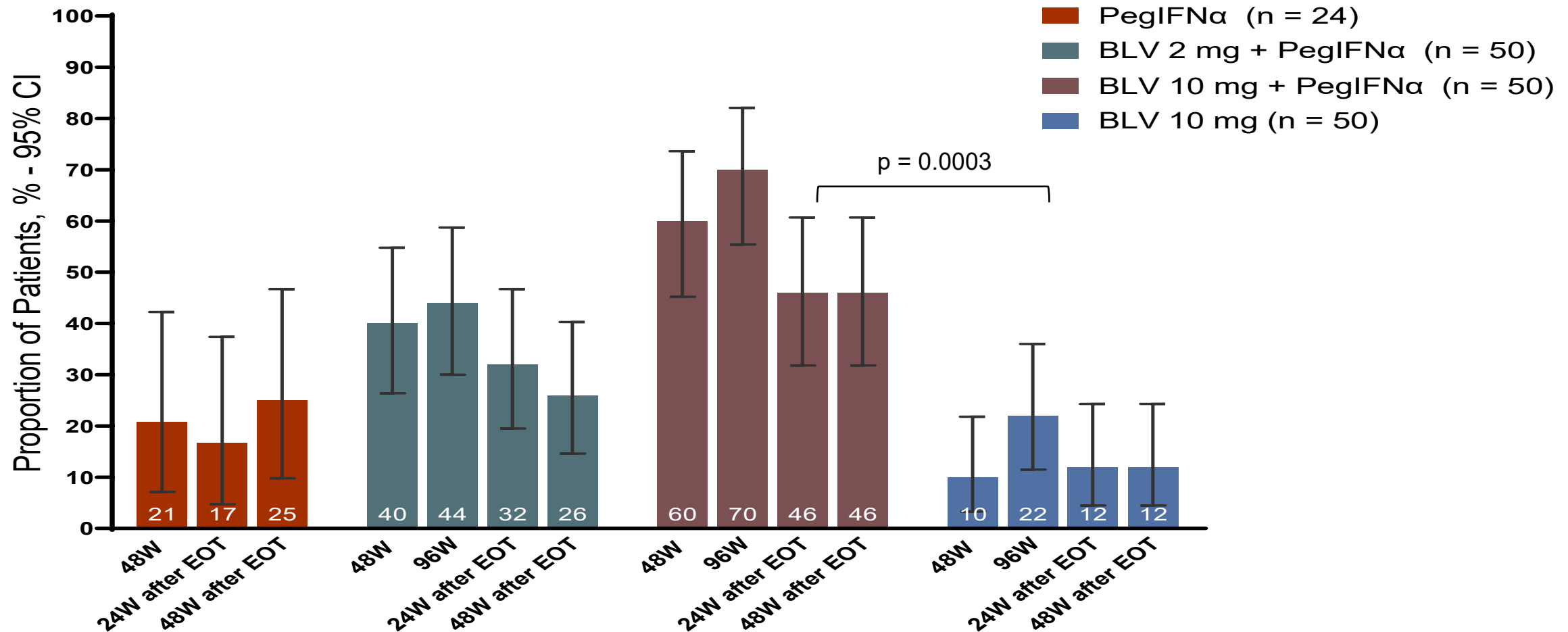


- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key Inclusion Criteria

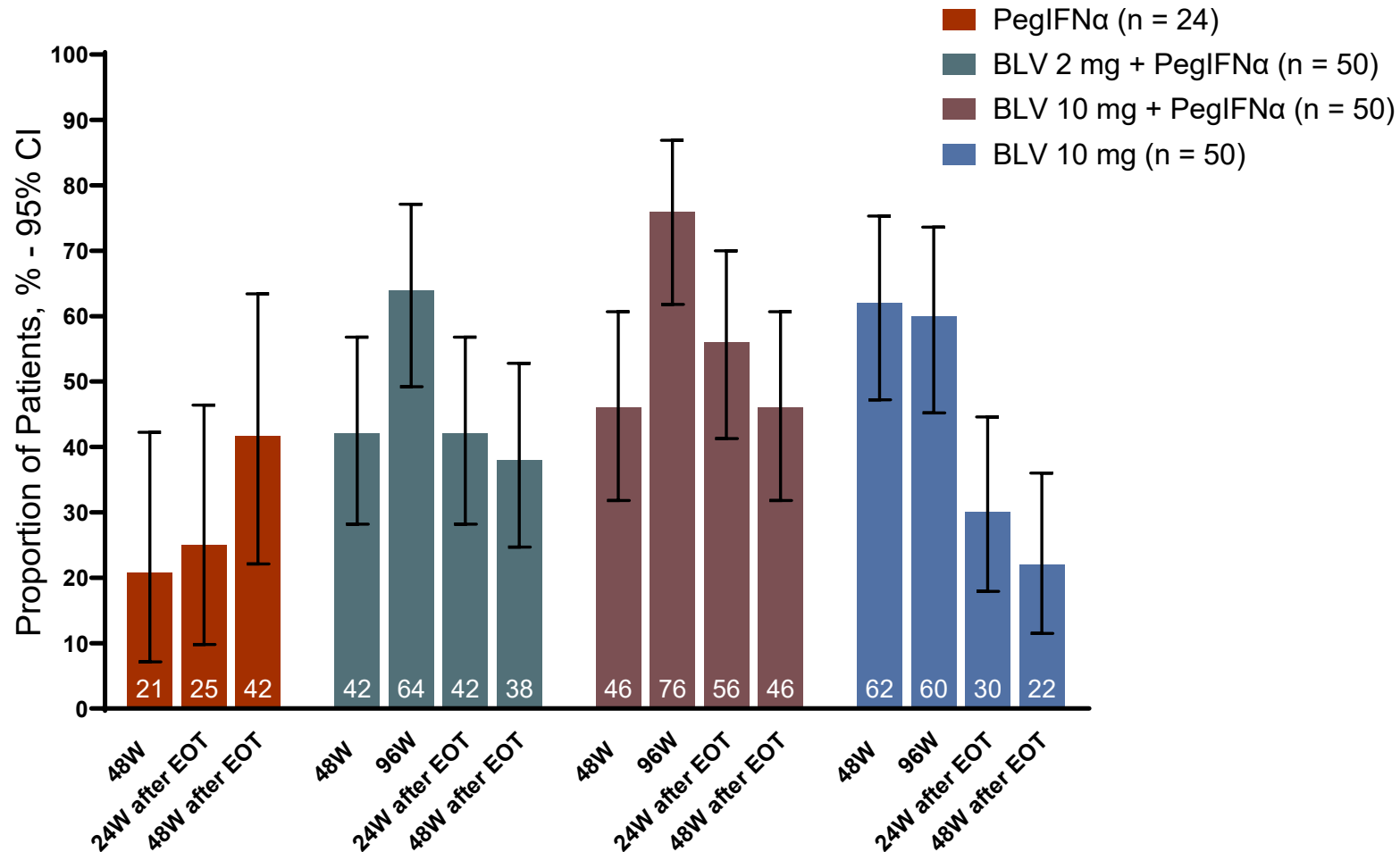
- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh (CTP) ≤ 6
- ALT $>1\times$ - $<10\times$ ULN; Platelets $\geq 90,000$ cells/mm³
- No IFN within 6 months before enrollment

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

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

HBsAg Endpoints At 48 Week after EOT

		PegIFN α n = 24	BLV 2 mg + PegIFN α n = 50	BLV 10 mg + PegIFN α n = 50	BLV 10 mg n = 50
HBsAg	HBsAg response*: $\geq 1 \log_{10}$ 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 PegIFN α
- Factors associated with HBsAg loss were at baseline non cirrhosis, non prior IFN therapy, Low HbsAg and HDV RNA levels

On-Treatment Safety

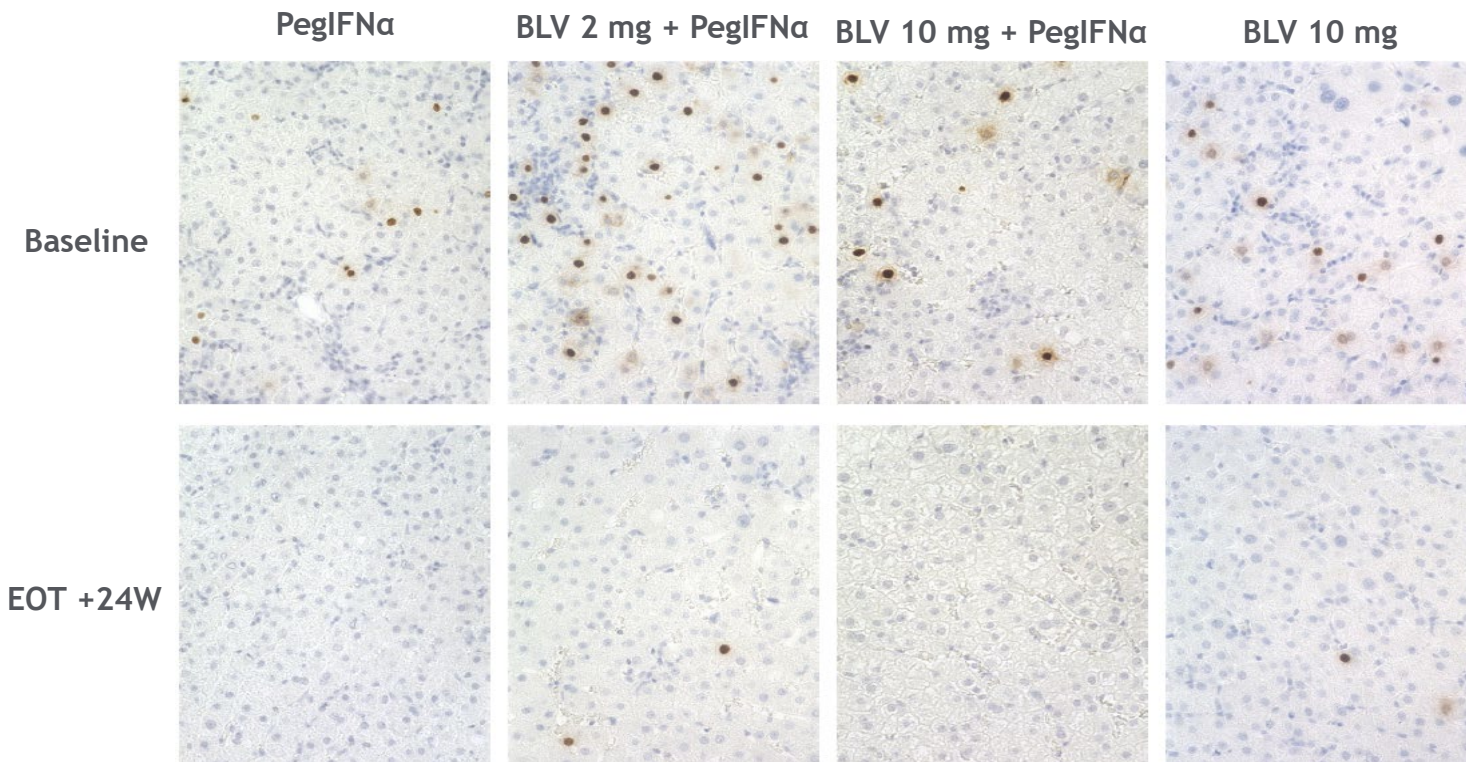
Treatment-Emergent Adverse Events, no (%)	PegIFN α n = 24	BLV 2 mg + PegIFN α n = 50	BLV 10 mg + PegIFN α n = 50	BLV 10 mg n = 50
Any AE	22 (92)	49 (98)	50 (100)	42 (84)
Any Grade 3-4 AE related to BLV	N/A	2 (4)	2 (4)	0
Any Grade 3-4 AE related to PegIFN α	13 (54)	26 (52)	26 (52)	N/A
Any SAE	3 (13)	3 (6)	8 (16)	2 (4)
Any SAE related to BLV	N/A	0	0	0
Any SAE related to PegIFN α	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 PegIFN α was consistent with the known safety profile of each drug
- Few Grade 3 TEAEs related to BLV, no SAE related to BLV

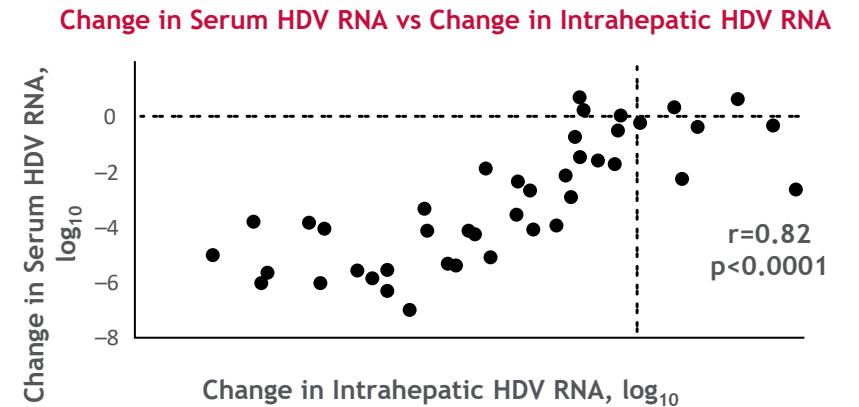
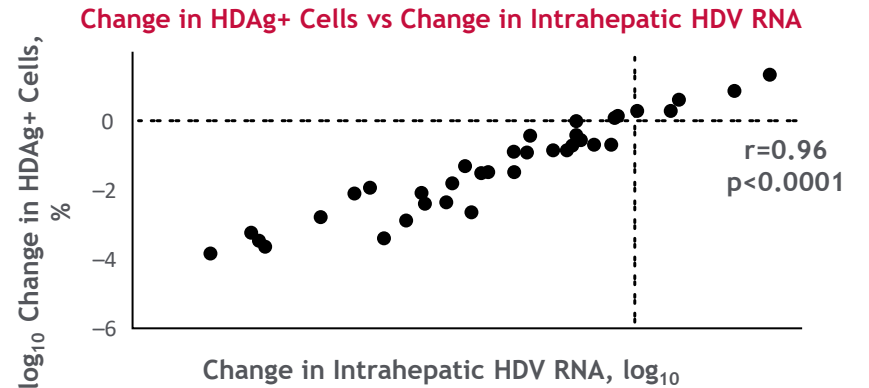
Intrahepatic Analysis of BLV + PegIFN α

Histological analysis of paired biopsies treated with BLV \pm PegIFN α (N=51)

Change in HDAg+ Cells (n=44)

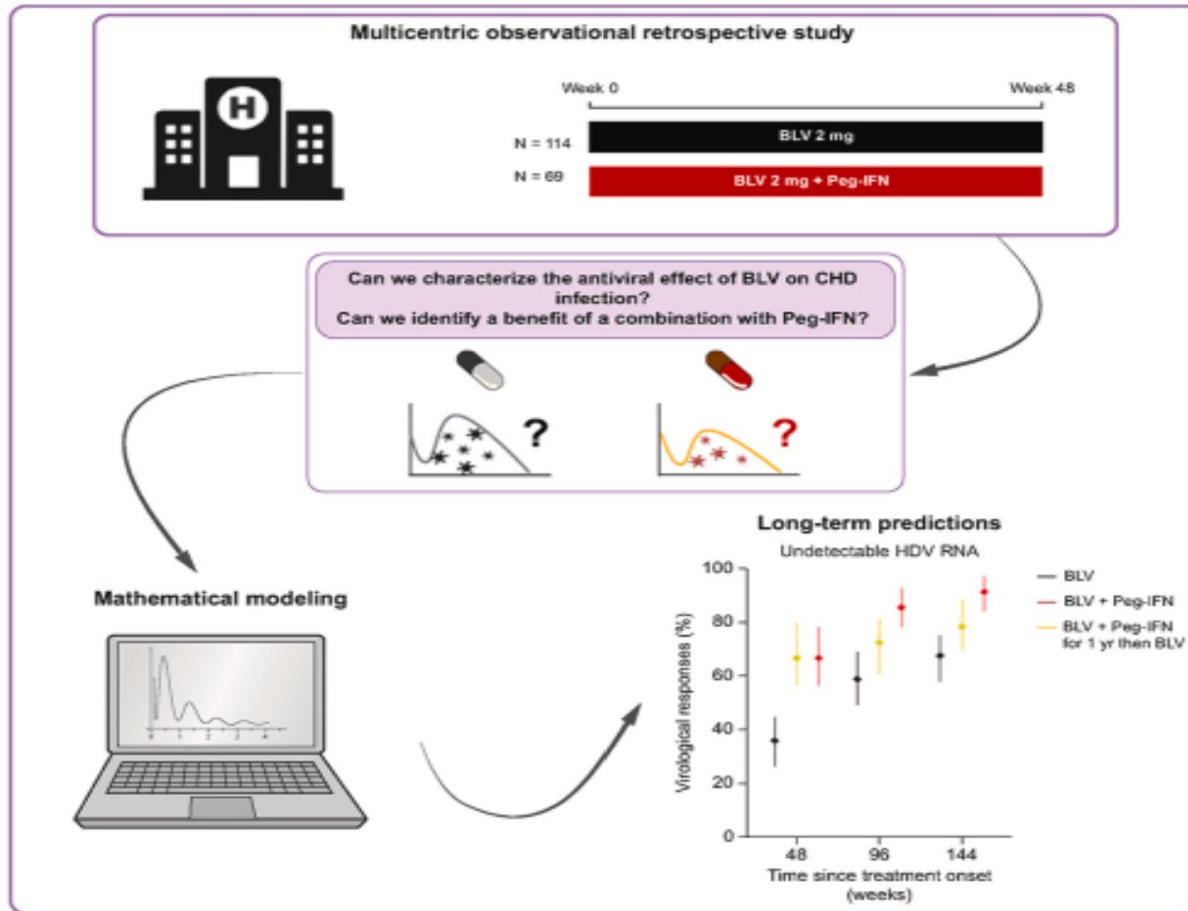


Correlation Analyses From BL to EOT +24W

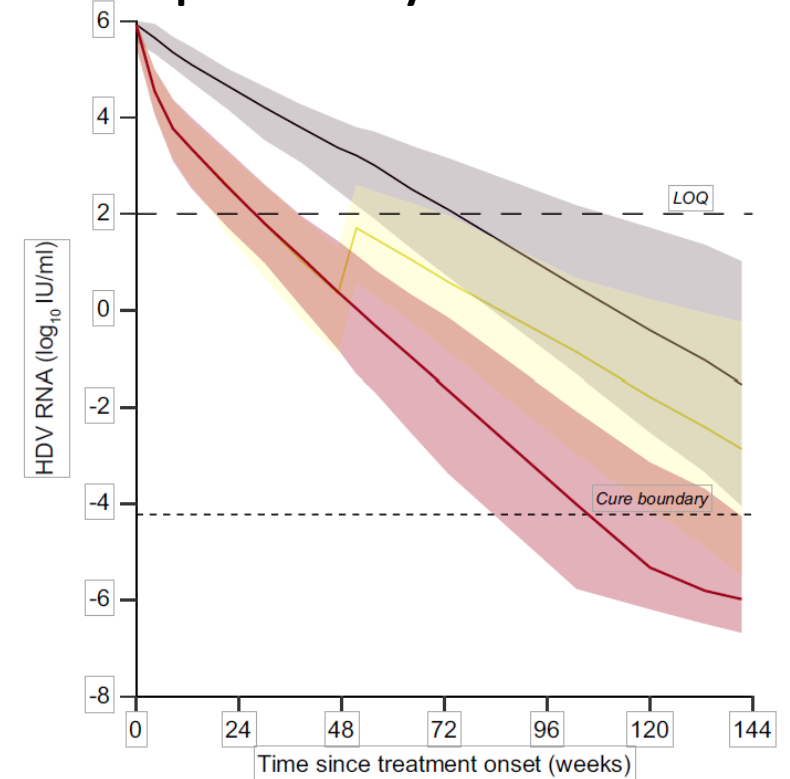


Intrahepatic and serum HDV RNA reductions are strongly correlated and reflect a reduction of infected cells

Real World data on the effect of Peg-IFN on the viral kinetics of patients with HDV treated with BLV



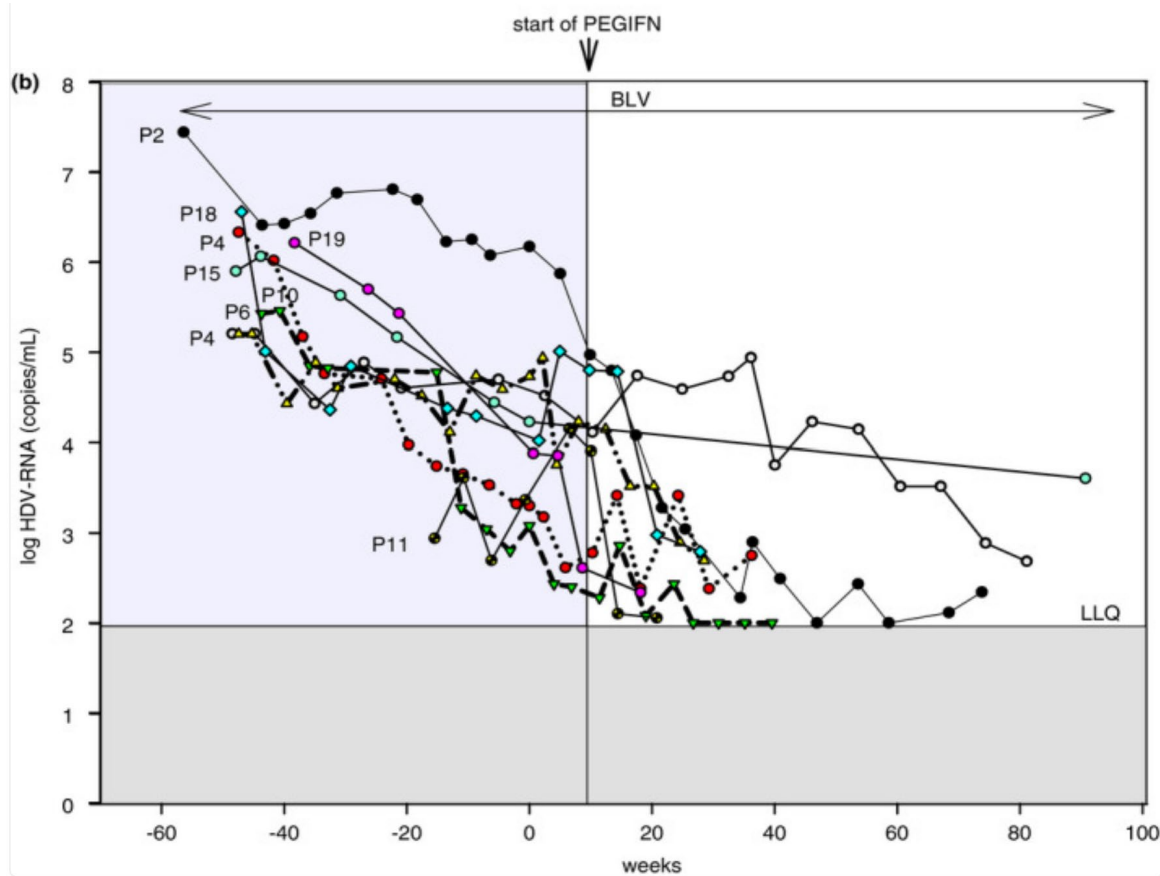
Viral kinetics predicted by the model



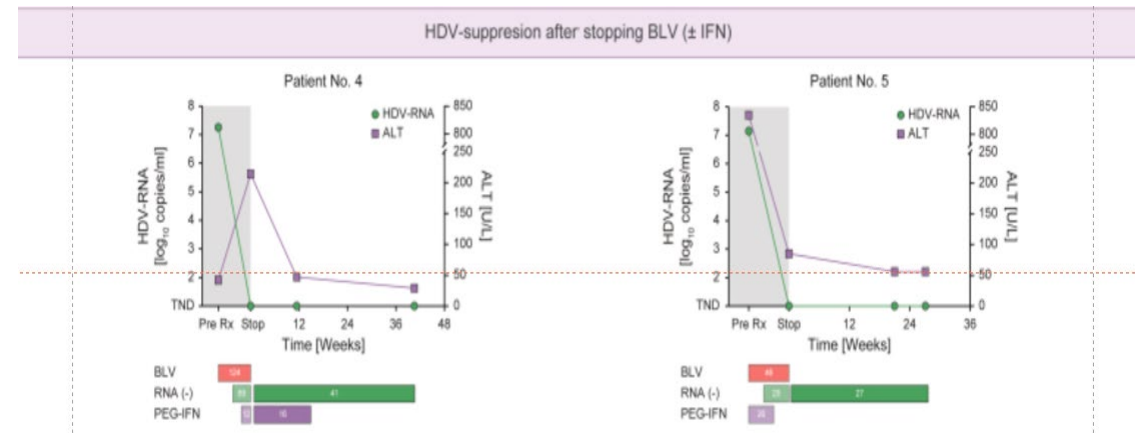
BLV (black) BLV+Peg-IFN (red), BLV + Peg-IFN, 48 wks+ BLV (yellow)

The addition of PegIFN to bulevirtide strongly increases viral kinetics

Role of Adding PegIFN in BLV non responders



Two achieved a complete response off therapy



Adding PegIFN to BLV, some partial or non virological response can achieved HDV RNA loss

Summary

BLV+PegIFN provides an opportunity for finite therapy

BLV 10 mg in combination with PegIFN α 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

Therapeutic Approaches for HDV therapy

Past

PegIFN

Currently

Bulevirtide (BLV)

BLV+PegIFN

Future

mAb antiHBsAg

- BJT-778

- Tobeivart ±
Elebsiran

Drugs for HBV

-siRNA

BJT-778, anti-HBsAg monoclonal antibody, achieved 100% virologic response in subjects with chronic hepatitis D (CHD): phase 2 study results



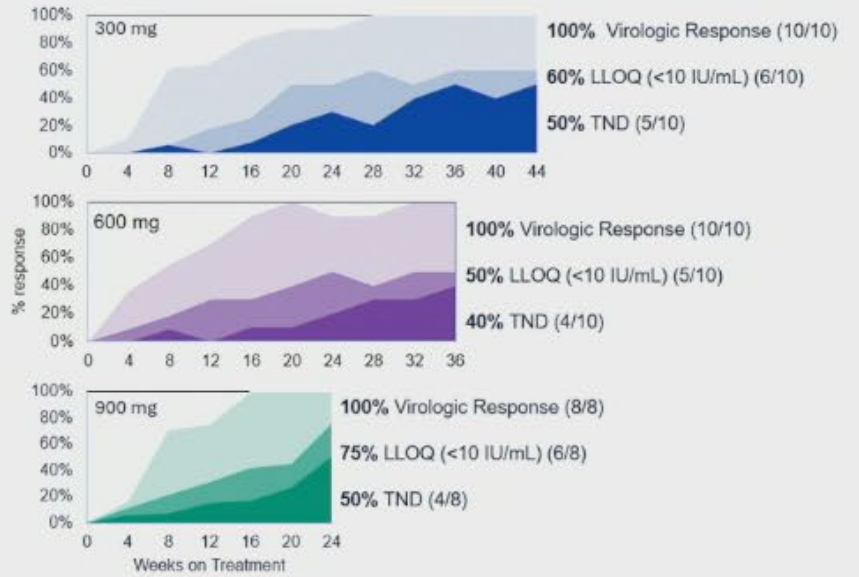
Background: BJT-778 is a fully human high-affinity anti-HbsAg monoclonal antibody that targets the antigenic domain of HbsAg; Removes HDV from blood and prevents HDV from infecting new hepatocytes by binding HbsAg.

Aim: To evaluate safety, virologic response, ALT normalization, and combined response in HDV patients

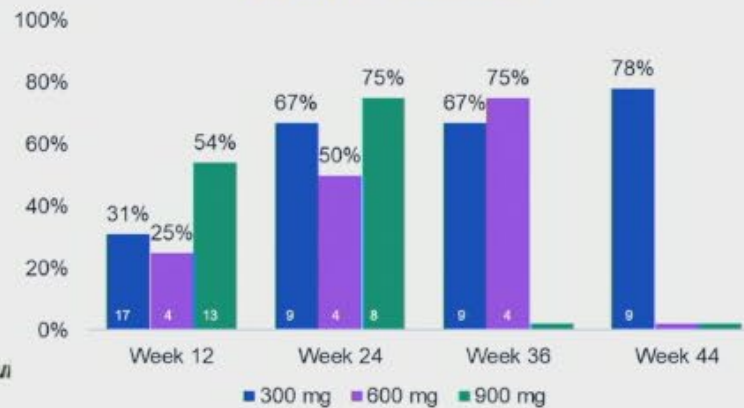
Methods: Enrolled up to 20 subjects in each Arm with primary endpoints being safety and tolerability. Inclusion criteria: detectable HDV RNA, HBV DNA 100 on nucs, compensated liver disease

Results: 47 subjects enrolled; 9%-44% cirrhosis in each arm;

No ≥ grade 3 AEs or SAEs



Combined virologic response and ALT normalization*



Conclusions: BJT-778 monotherapy is safe and well tolerated and shows promising efficacy in CHD



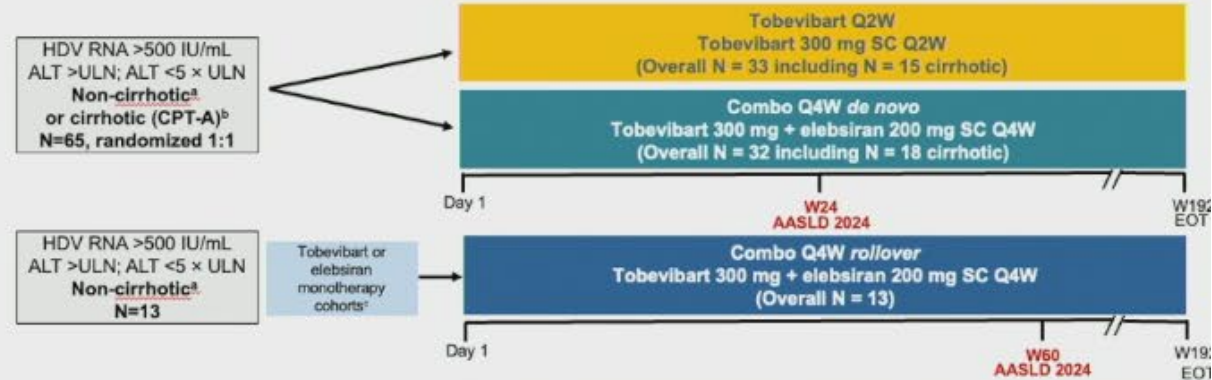
Efficacy and safety of tobevibart (VIR-3434) alone or in combination with elebsiran (VIR-2218) in participants with chronic hepatitis delta virus infection: Week 24 primary endpoint analysis from the Phase 2 SOLSTICE trial



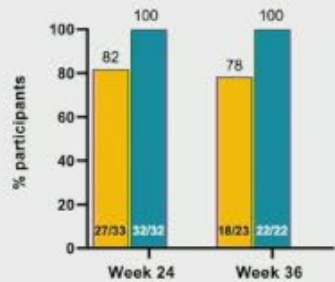
Background: The agents tobevibart (mAb) and elebsiran (siRNA) have complementary antiviral/immunomodulatory effects for functional cure

Methods: Randomized 1:1 to either mono or combo therapy vs rollover

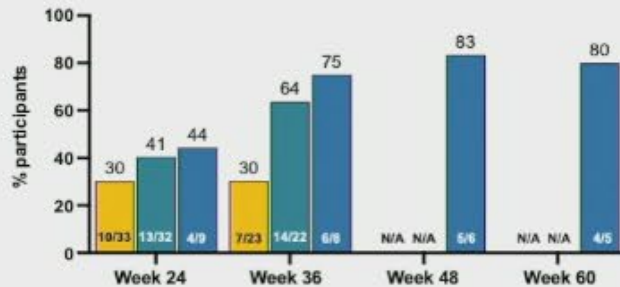
Results: 78 subjects randomized; 46%/ 56% cirrhotic in mono and combo arms



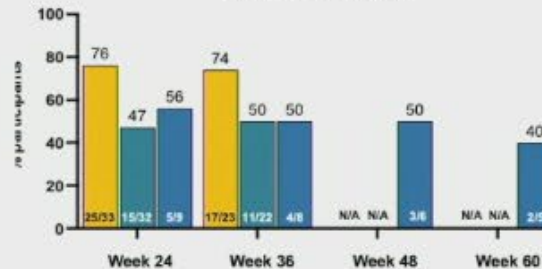
HDV RNA ≥ 2 log₁₀ decrease or HDV RNA <LOD
Protocol defined endpoint



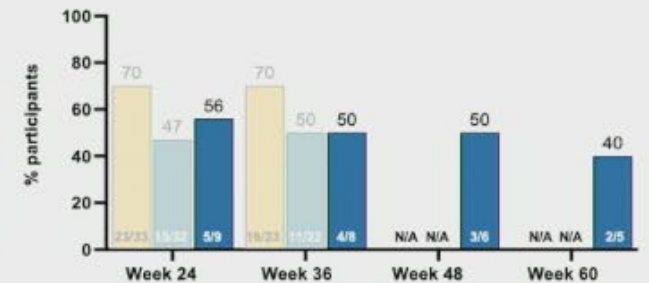
HDV RNA <LLOQ, TND



ALT Normalization



HDV RNA ≥ 2 log₁₀ decrease or HDV RNA <LOD + ALT Normalization



Similar HDV RNA/ ALT responses in cirrhotic/ non-cirrhotic

- Most TEAEs were mild

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Asselah T, et al, Abstract 74

Conclusions: Tobevibart/ elebsiran may serve as a novel treatment regimen for HDV. Combo of tobevibart + elebsiran showed greater reductions in HBsAg levels than tobevibart monotherapy. Phase 3 trial to start 2025.

Summary

Therapy for Chronic Hepatitis D is evolving

BLV is the current standard of care

Best therapeutic regimen needs to be defined (dose, duration, combination.....)

New drugs defined as a breakthrough therapy are in phase III