HDV: il punto sulle nuove opzioni terapeutiche

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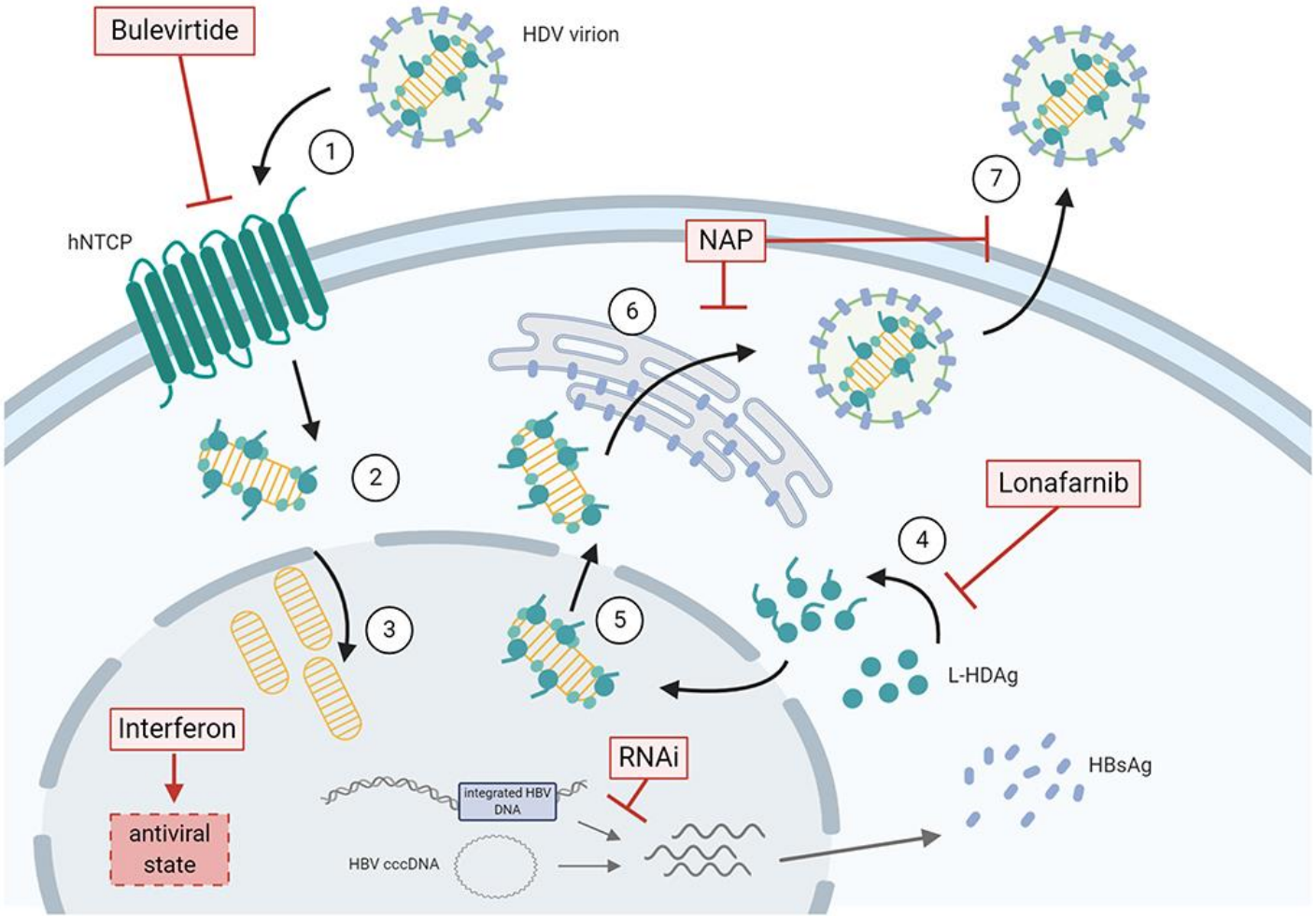
Disclosures

Speakers Bureau: Gilead, AstraZeneca
Advisory: Gilead, Janssen, Roche, EISAI-MSD

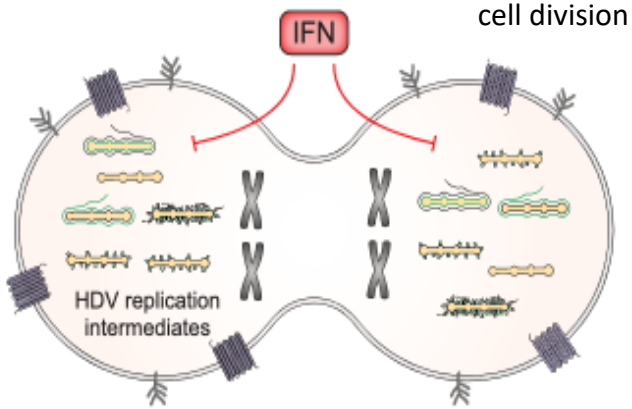
Old and new targets for HDV infection control and CHD cure

- A florid HDV infection requires an ogoing and transcriptionally active HBV infection, as **HDV uses HBsAg to egress from and to re-enter into hepatocytes**
- However, during liver regeneration, **HDV-RNA can be transmitted to dividing cells in absence of HBV**
- **HDV uses the cellular machinery for the transcription of its viral RNA**



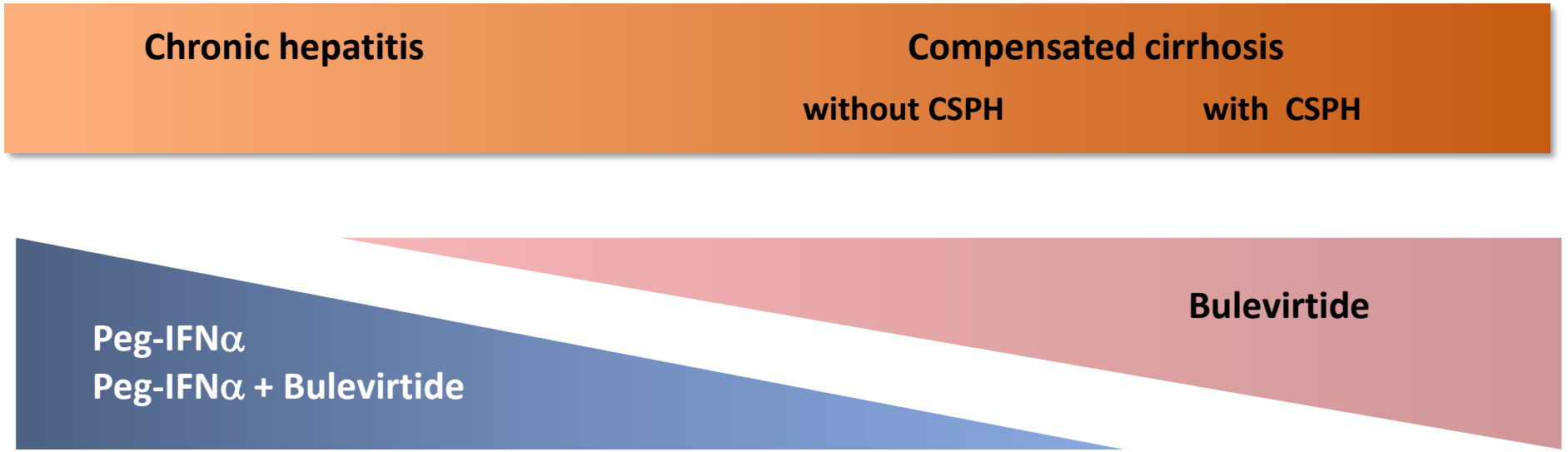
- **Entry inhibitors**
- **Prenilation inhibitors**
- **IFNs α and λ**
- **Treatments to reeduce HBsAg production** (siRNA, NAPs, mAb targeting a HBsAg)

cell division mediated spread



Sandmann L et al, J Hep 2021; Zhang Z et al J Hep 2021

Treatment of Chronic Hepatitis Delta



Finite treatment

To cure the infection/disease

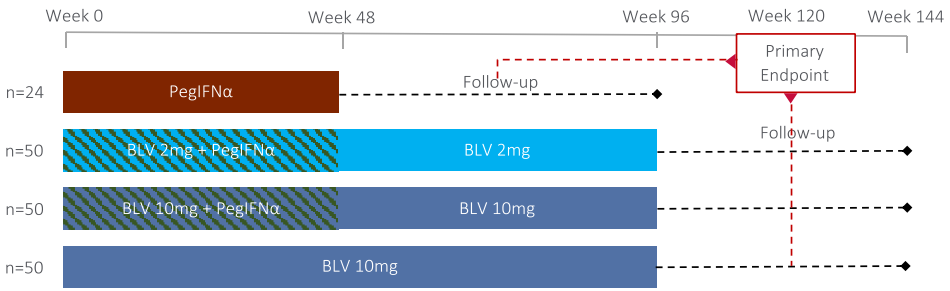
Prolonged treatment

To control the infection/disease

Additional factors influencing the treatment schedule

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

Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta: Primary Endpoint Results from a Phase 2b Open-Label, Randomized, Multicenter Study MYR204



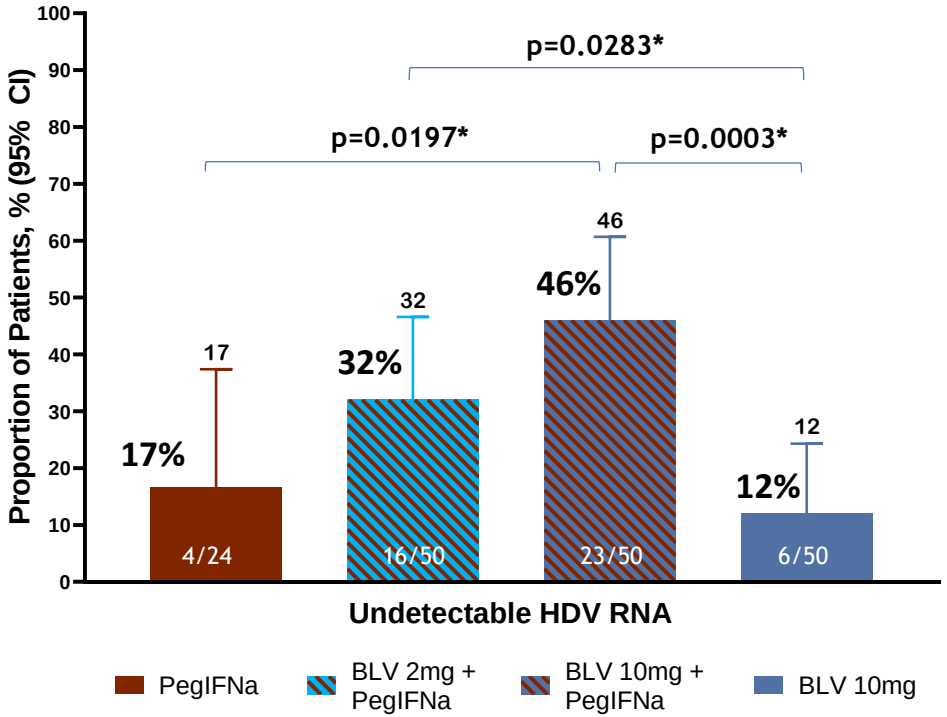
Key Inclusion Criteria

- CHD with detectable serum HDV RNA
- Without cirrhosis or with cirrhosis; Child-Turcotte-Pugh (CTP) ≤6
- ALT >1x - <10x ULN
- No IFN within 6 months before BL

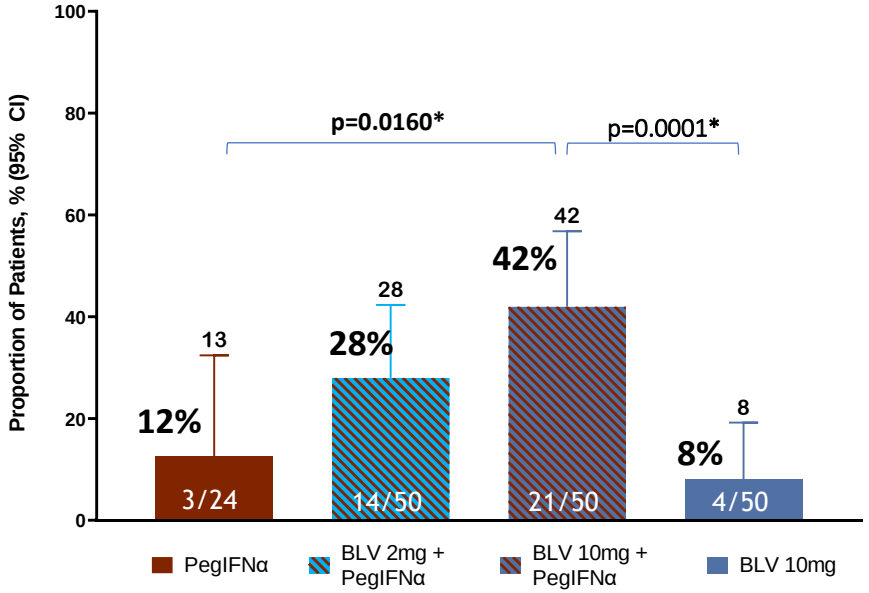
Primary end point

- **Undetectable HDV-RNA at week 24 after EOT**

HDV RNA undetectable at Week 24 after EOT

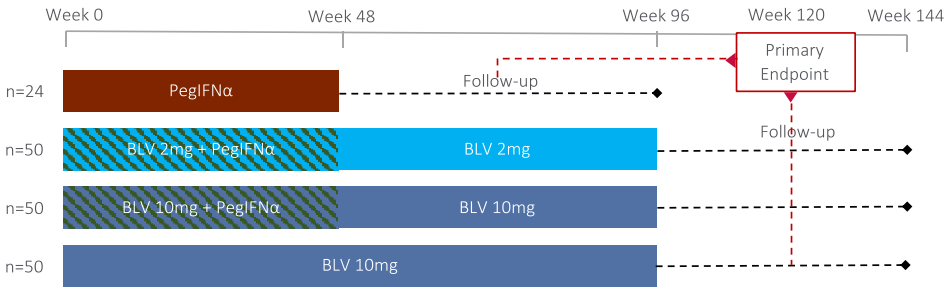


Composite Response (HDV RNA Undetectable + ALT Normalization) at Week 24 after EOT



Asselah T et al, AASLD 2023

Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta: Primary Endpoint Results from a Phase 2b Open-Label, Randomized, Multicenter Study MYR204



Key Inclusion Criteria

- CHD with detectable serum HDV RNA
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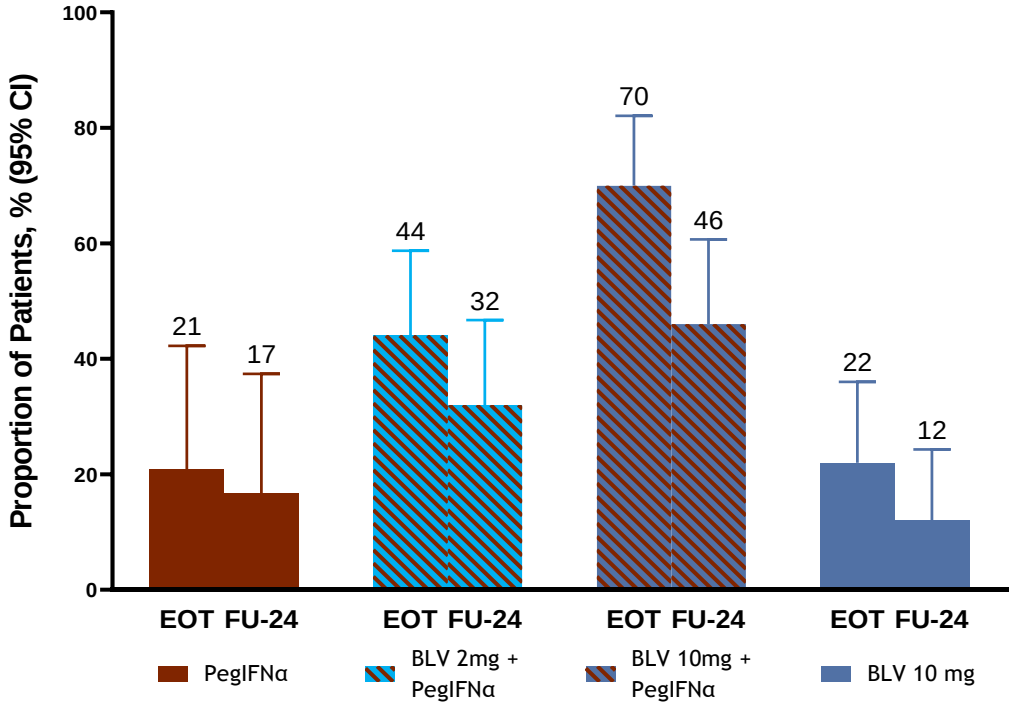
- ALT >1x - <10x ULN
- No IFN within 6 months before BL

Primary end point

- **Undetectable HDV-RNA at week 24 after EOT**

HBsAg loss: in 6 patients treated with Peg-IFN + BLV 2 mg (2) or 10 mg (4)

Undetectable HDV RNA at EOT vs Week 24 after EOT

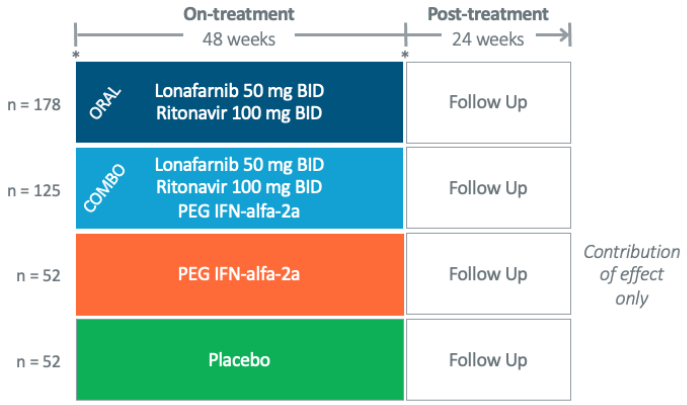


Assessment of the durability of undetectable HDV RNA at 48 weeks after EOT is planned

Asselah T et al, AASLD 2023

Week 48 Results of the Phase 3 *D-LIVR* Study: a Randomized Double-Blind, Placebo-Controlled Trial, Evaluating the Safety and Efficacy of Lonafarnib-Boosted with Ritonavir with or without Peginterferon Alfa in Patients with Chronic Hepatitis Delta

Ohad Etzion et , ILC 2023

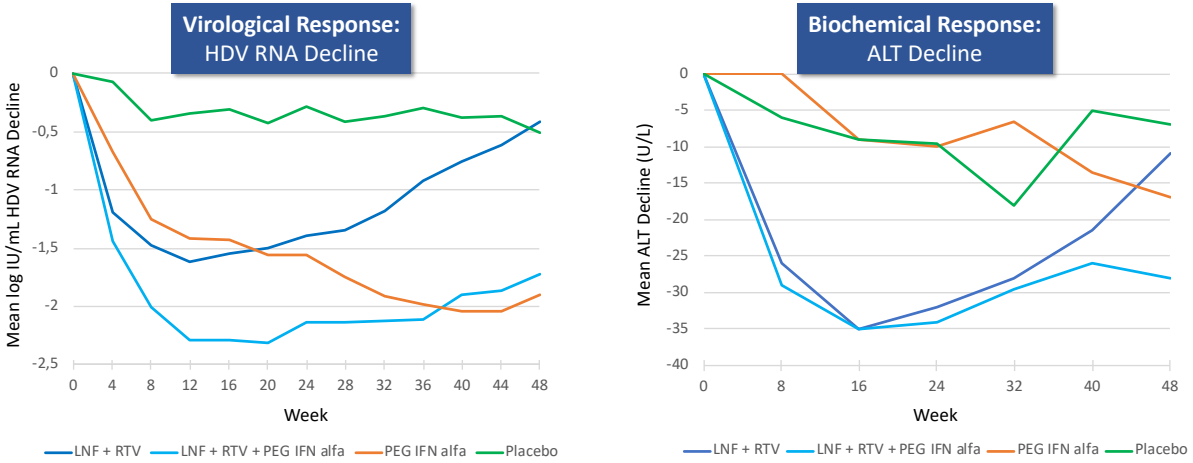


- 405 CHD patients with compensated liver disease
- ALT > 1.3 x - <10 x; HDV-RNA > 500 IU/ml; HBV-DNA < 20 IU/ml

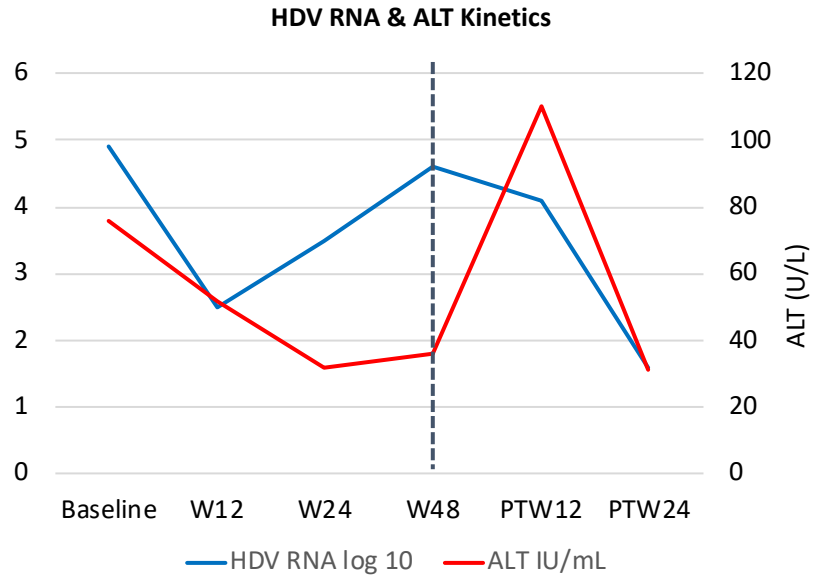
Primary endpoint (week 48): ≥ 2 log HDV-RNA decline + normal ALT
Secondary endpoint (week 48): no worsening in fibrosis + ≥ 2 point in Ishak HAI score

Mean HDV RNA and ALT Decline Through End of Treatment

INTENT TO TREAT (ITT) POPULATION (N=405)

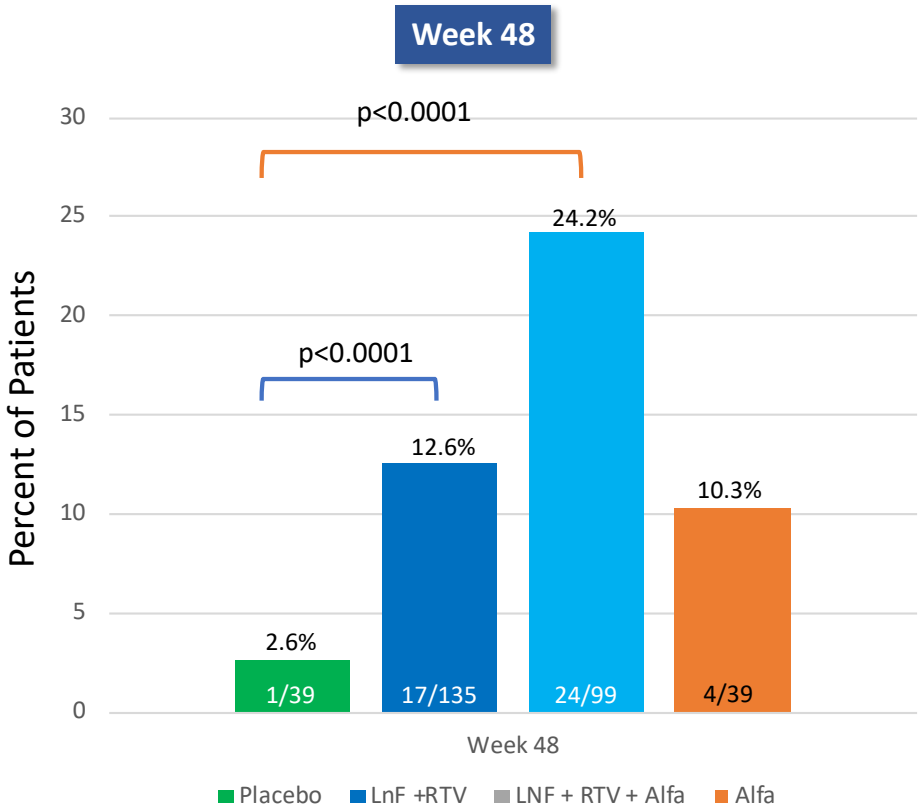


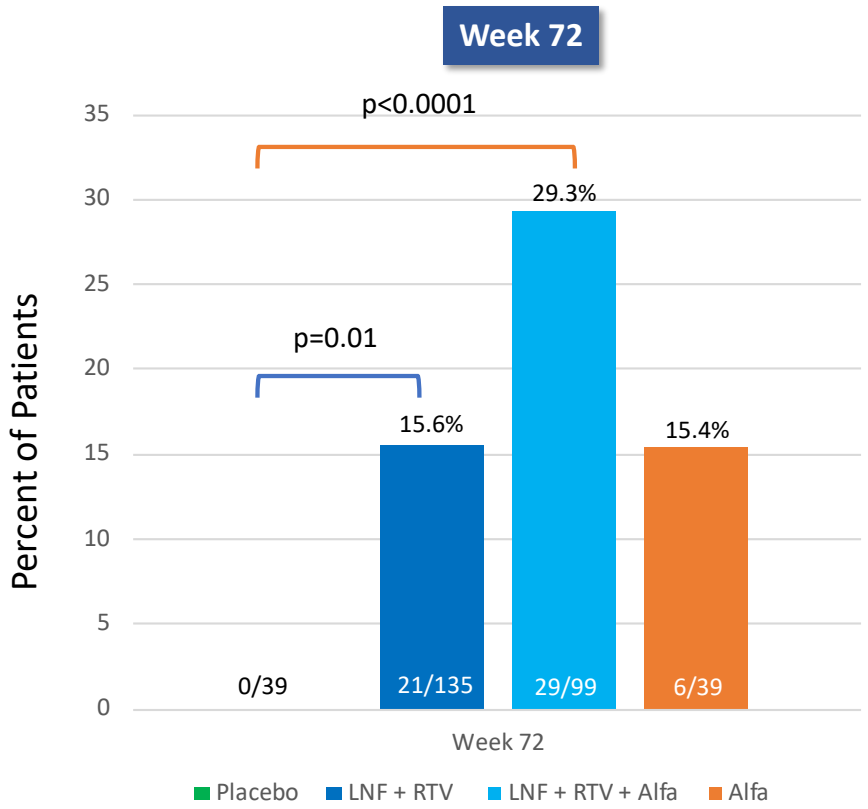
W12 of therapy seems the timepoint after which the kinetics of viral response diverges between responders and non-responders at week 48



Post treatment ALT flares occured in approximately 10% of the all oral and 20% of the combo arm

Week 48 Results of the Phase 3 *D-LIVR* Study: a Randomized Double-Blind, Placebo-Controlled Trial, Evaluating the Safety and Efficacy of Lonafarnib-Boosted with Ritonavir with or without Peginterferon Alfa in Patients with Chronic Hepatitis Delta





- Both LNF arms achieved the composite primary endpoint vs placebo
- In the combination arm a significant improvement in histology was observed

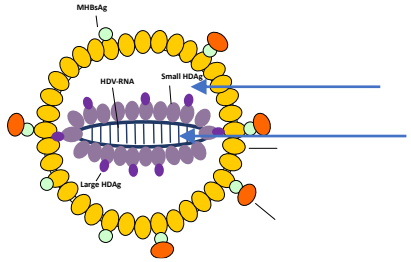
24-week off-treatment response rate exceeds EOT response rates, suggests finite, oral-based therapy may be possible in a subset of CHD patients

Ohad Etzion et , ILC 2023

Nucleic Acid Polimers - REP 2139-Mg

Passage through secretory pathway (transient)

- Targets the host HSP40 chaperone DNAJB12
- Blocks HBV SVP assembly
- Blocks envelopment of HDV RNP



Accumulation in nucleus (progressive with continued dosing)

- Targets S-HDAg and L-HDAg
- Inhibits replication / morphogenesis of HDV upstream of RNA envelopment

REP 2139-Ca
500mg qW **IV** 15 weeks

REP 2139-Ca
250mg qW **IV** 15 weeks

Pegylated interferon α-2a
180 µg qW SC 48 weeks

•12 Caucasian patients with confirmed chronic HBV / HDV co-infection
•All were HBeAg negative , with negative or low HBV DNA, Chronic HDV without cirrhosis, baseline serum HBsAg > 1000 IU/ml treatment duration : 63 weeks

Patients entered into trial		12
End of treatment HBsAg response	> 1 log below baseline	9
	< 1 IU/mL	6
	<0.05 IU/mL	5
HDV RNA response	> 5 log below baseline	12
	target not detected	11
Patients currently completed treatment and ≥ 1.5 years of follow-up		**11**
HBsAg ≤ LLOQ		4 (3 @ FW2Y)
HBV DNA < LLOQ		6 (5 @ FW2Y)
HDV RNA target not detected		7 (6 @ FW2Y)

At 1 year follow-up:

7/11 (65%) HDV RNA TND, 9/11 (82%) >2 log10 reduction

- 8 with normal ALT/AST
- 5 with declining or normal hepatic stiffness
- 5 with HBsAg ≤ LLOQ
- 5 with HBV DNA < LLOQ

At 3,5 years follow-up:

7/11 (65%) HDV RNA TND, 9/11 (82%) >2 log10 reduction

- 8 with normal ALT/AST
- 6 with declining or normal hepatic stiffness
- **4 with HBsAg ≤ LLOQ**
- 5 with HBV DNA < LLOQ

The establishment of HDV functional cure and HBV virologic control/functional cure and HBsAg seroconversion are durable over 3.5 years

Bazinet M et al. Lancet GH 2017; 2: 877-889 Bazinet M et al Hepatol Comm. 2021 Fonte et al., HBV meeting 2023

REP 2139-Mg in HDV compensated cirrhosis and BLV failure

48 weeks with REP 2139-Mg 250 mg SC QW + TDF 245 mg PO QD + with PEG-IFN 90µg SC QW (only with compensated cirrhosis and if no contra-indication)

Virologic response during therapy								
Virologic response	Duration of therapy							
	1-4 weeks (n=15)	5-8 weeks (n=15)	9-12 weeks (n=14)	13-24 weeks (n=12)	24-48 weeks (n=9)	> 48 weeks (n=2)*	Removal of NAP + pegIFN (n=2)	Removal of TDF (n=1)
Any HDV RNA decline from baseline	5	8	8	7	7	2	2	1
HDV RNA ≥ 2 $\log_{10}$ decline from baseline	3	6	7	6	7	2	2	1
HDV RNA < LLOQ	2	4	4	5	5	2	2	1
HDV RNA target not detected	1	1	2	5	5	1	2	1
Any HBsAg decline from baseline	1	3	6	7	7	2	2	1
HBsAg > 1 $\log_{10}$ decline from baseline		1	4	6	6	2	2	1
HBsAg > 2 $\log_{10}$ decline from baseline		1	3	5	4	2	2	1
HBsAg < 10 IU/mL			2	3	4	1	2	1
HBsAg < 0.05 IU/mL				3	2	1	2	1
Anti-HBs seroconversion			1	2	2	1	2	1
ALT normal				3	7	1		

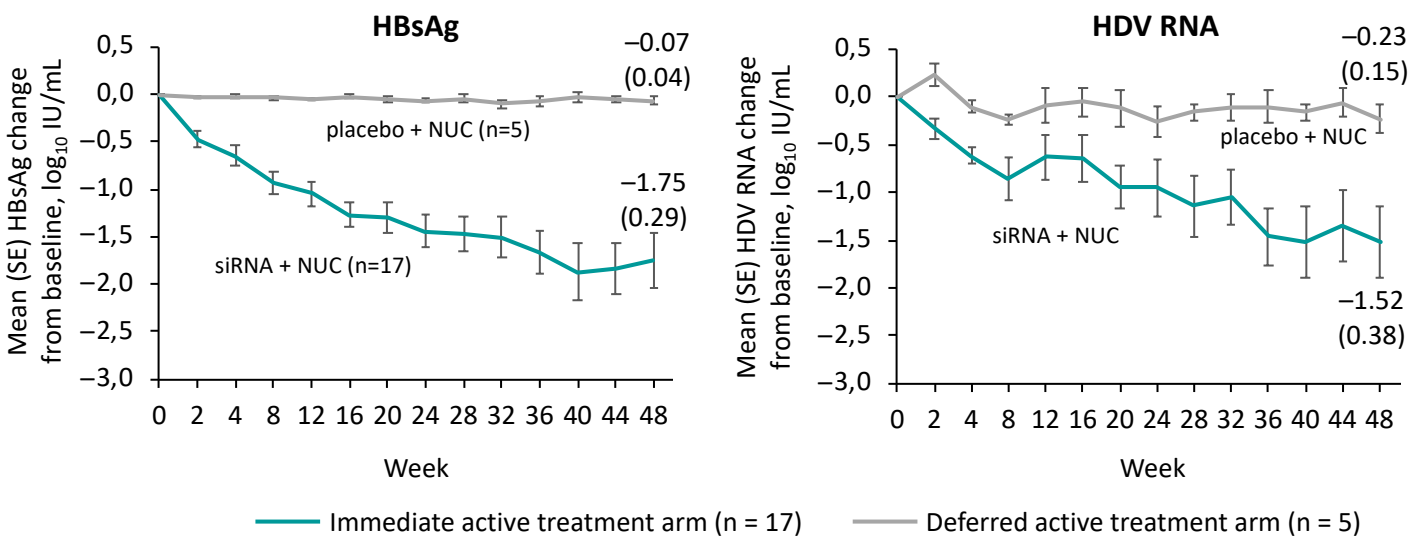
7/9(78%) VR
5/9 (56%) TND
7/9 (78%) CR
2/9 (22%) HBsAg loss

- One patient extended with HDV RNA TND but clearance of HBsAg had not occurred at 48 weeks (HBsAg loss occurred at week 68)
- One patient extended with increased dosing with 2 $\log_{10}$ decline of HDV RNA with detectable HBsAg at week 48.

Bourliere M et al, Stiges 2023

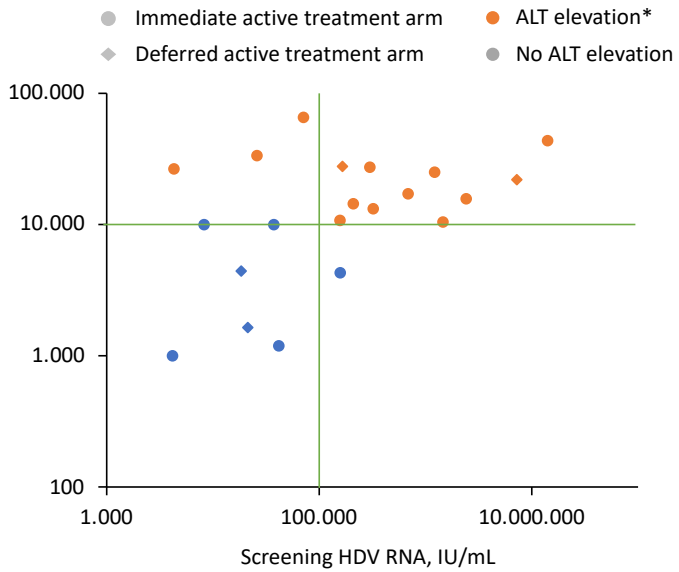
REEF-D study (part 1): siRNA JNJ-73763989 plus NUC in CHD - HBsAg, HDV RNA, ALT levels

- 22 CHD patients were enrolled in the study and 17 entered the active arm (treatment with JNJ-73763989 plus NA for 48 weeks)
- At **week 48** the **mean HBsAg and HDV-RNA declines were of 1.75 and 1.52** log10 IU/ml and a simultaneous decline of the 2 viral markers was observed



- 4/17 (23.5%) of the patients achieved at week 48 both >2 log HDV-RNA decline and normal ALT (primary endpoint)
- 5 patients without ALT elevation experienced a continuous HDV-RNA decline and 80% of them achieved the primary endpoint

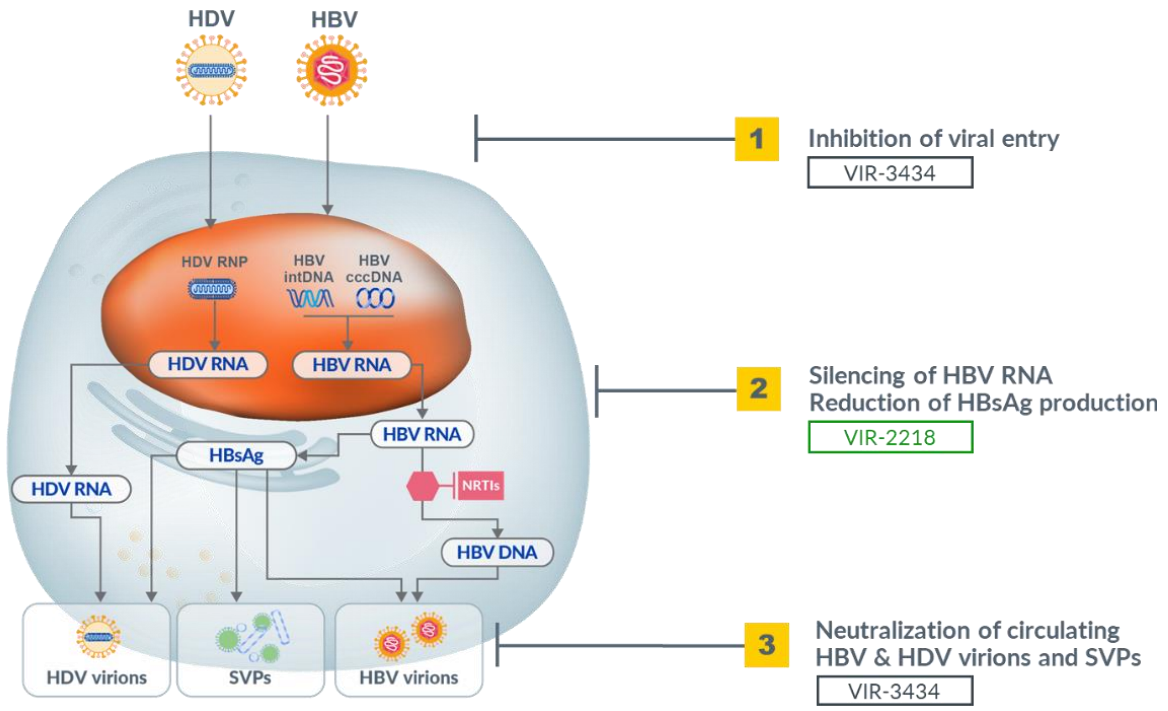
ALT flares according to BL HBsAg and HDV-RNA

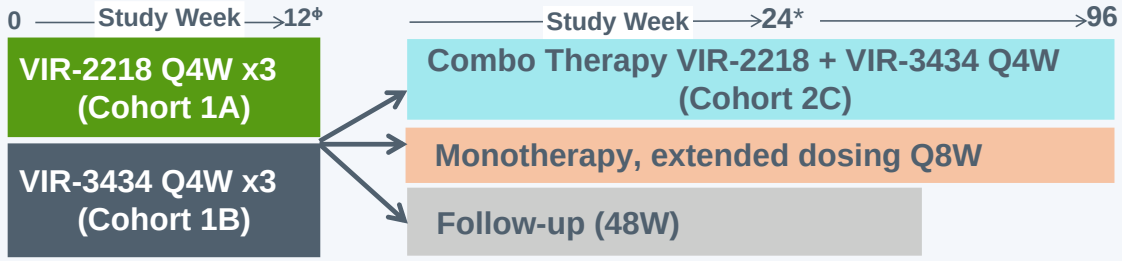


- **12/17 (70.6%) patients experienced an ALT increase (from week 8 to 20) leading to treatment discontinuation → the ALT elevations was associated with on-treatment rebound of HDV-RNA**
- ALT flares, predominantly in patients with high HBsAg and HDV RNA levels at baseline, led to exclusion of patients with cirrhosis or HBsAg >10,000 IU/mL and HDV RNA >100,000 IU/mL

H. Wedemeyer et al. ILC-2023 OS-030

The monoclonal antibody VIR-3434 and siRNA VIR-2218 for the treatment of chronic Hepatitis D Virus: preliminary results from the Phase 2 SOLSTICE trial





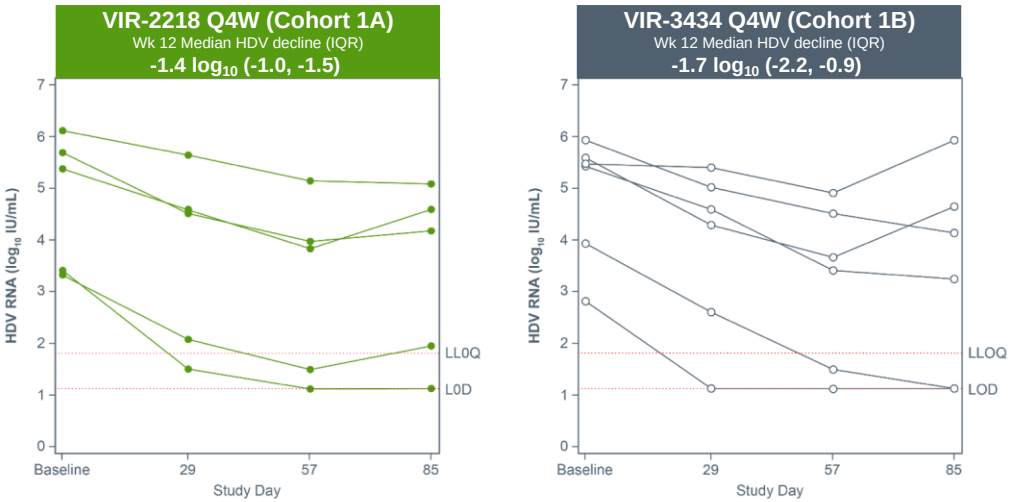
- Participants not achieving ALT normalization and virologic response at Week 12 can start combination therapy or follow up.
- Participants achieving combined endpoint at Week 12 transition to extended dosing (Q8W) monotherapy

VIR-3434 also has the **potential to activate the immune system**:

- due to specialized mutations in the Fc domain (enhancing binding to the FcR Iia activating receptor), VIR-3434 has the potential to **act as a T cell vaccine**. VIR-3434 is designed to capture virions and SVPs, deliver such virons and SVPs to DCs, and instruct these DCs to mature and stimulate T cells to mature and stimulate T cells that can eliminate HBV infected hepatocytes.
- VIR-3434 has the potential to **act via ADCC** (antibody dependent cellular toxicity): by binding to HBsAg at the cell surface, it recruits NK cells to eliminate infected hepatocytes. The Fc domain of VIR-3434 has been engineered to promote ADCC.
- by **reducing the amount of HBsAg in the blood**, VIR-3434has the potential to remove a brake on the immune system by decreasing the ability of HBV to suppress it.

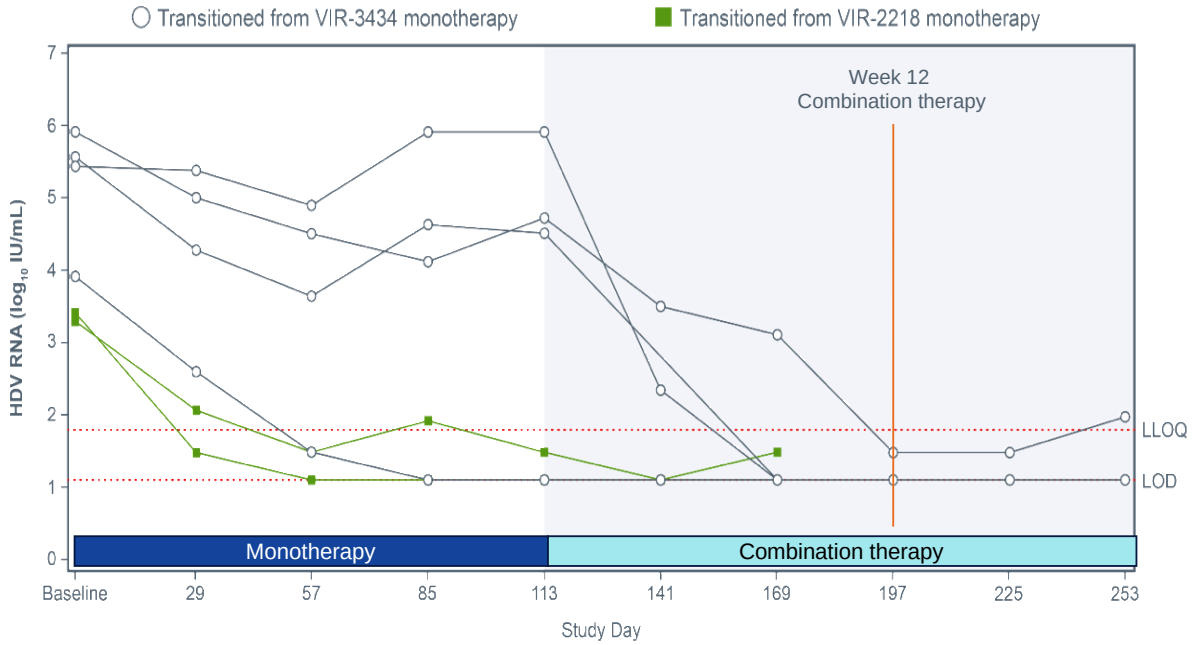
Asselah T et al AASLD 2023

The monoclonal antibody VIR-3434 and siRNA VIR-2218 for the treatment of chronic Hepatitis D Virus: preliminary results from the Phase 2 SOLSTICE trial



- ALT elevations >300 U/L in siRNA monotherapy occurred in participants with baseline HBsAg > 10,000 IU/mL
- No ALT elevations have been observed to Week 20 with mAb monotherapy or siRNA + mAb (VIR-2218+VIR-3434) combination therapy regardless of baseline HBsAg or HDV RNA.

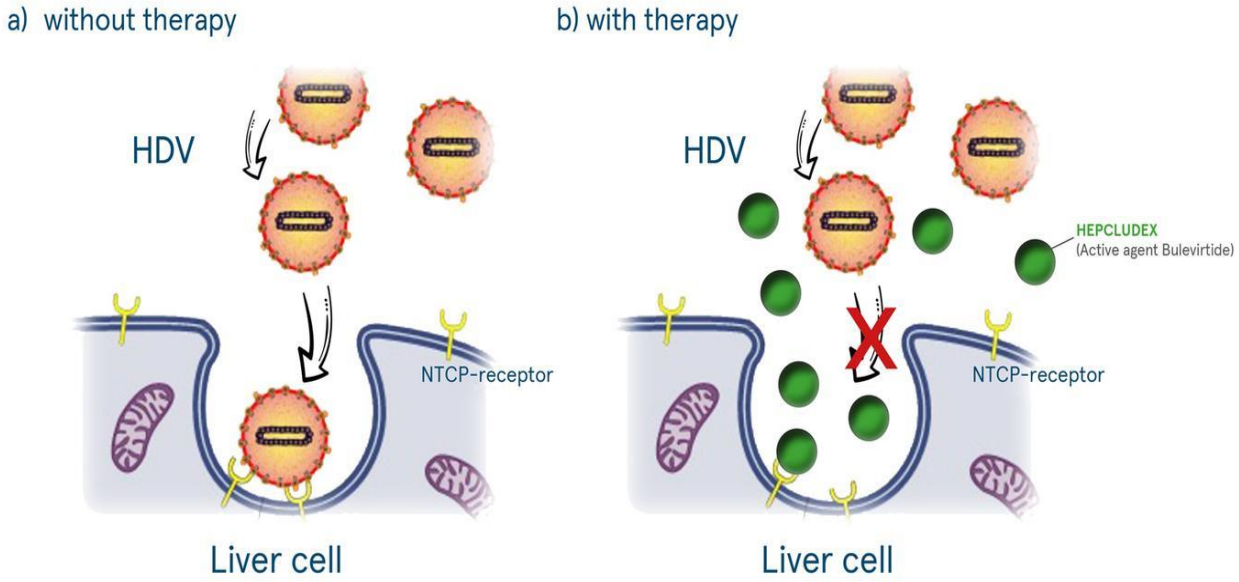
Antiviral activity of combination VIR-2218 and VIR-3434 therapy (Cohort 2C)



- Early data demonstrate tolerability and potent antiviral activity after 12 weeks of VIR-2218 + VIR-3434 combination therapy.
- Combination therapy achieved the greatest and fastest decline in HDV RNA observed with any therapy to date

Asselah T et al AASLD 2023

Bulevirtide (BLV) is the first-in-class entry inhibitor



Mode of action:

- BLV is a **synthetic N-acetilated pre-S1 derived lipopeptide that inhibits HBV entry into hepatocytes** in vitro and in vivo, by blocking NTCP, the entry receptor for HBV/HDV
- **New infections and viral spread in the liver prevented**.
- Proliferating virus-free hepatocytes should recolonize the liver, eliminating HBV ccc-DNA and hepatitis D

.

Administration:

- Daily, self administered s.c. injections

The EMA conditional marketing authorisation was switched to a standard marketing authorisation on 18.07.2023.

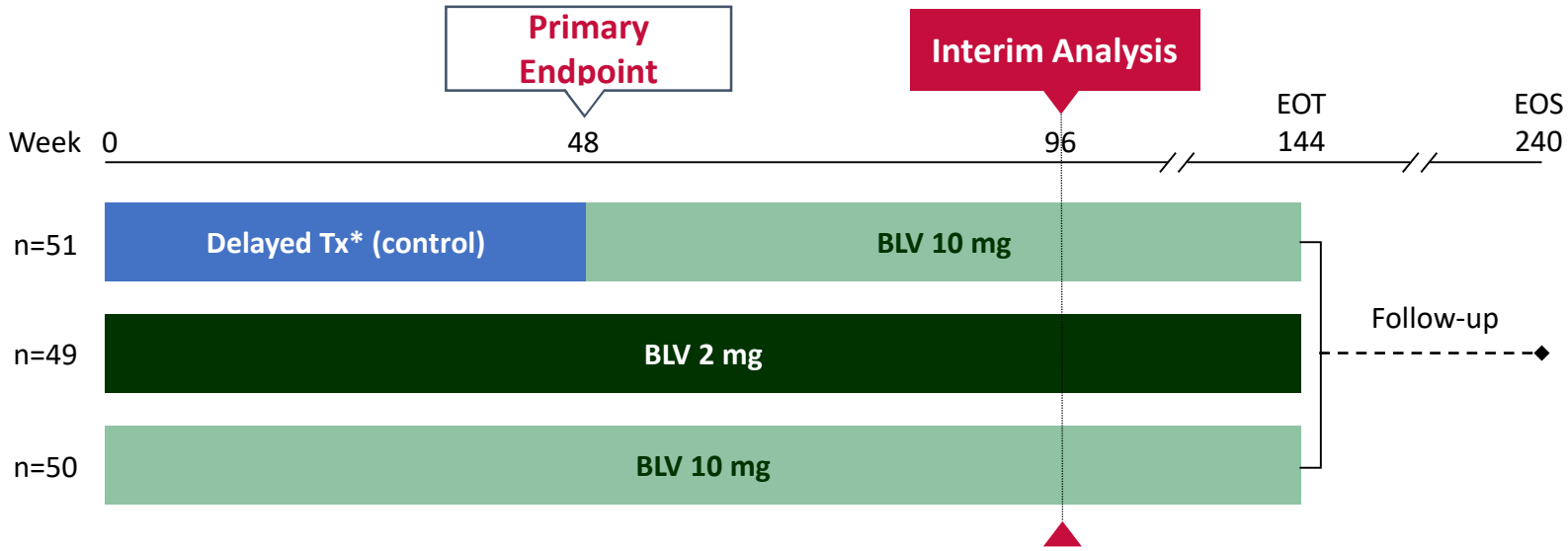
Lemp and Urban S, 2014 ;*SUMMARY OF RISK MANAGEMENT PLAN FOR HEPCLUDEX (BULEVIRTIDE) _EMA

MYR301 Study Design: a 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

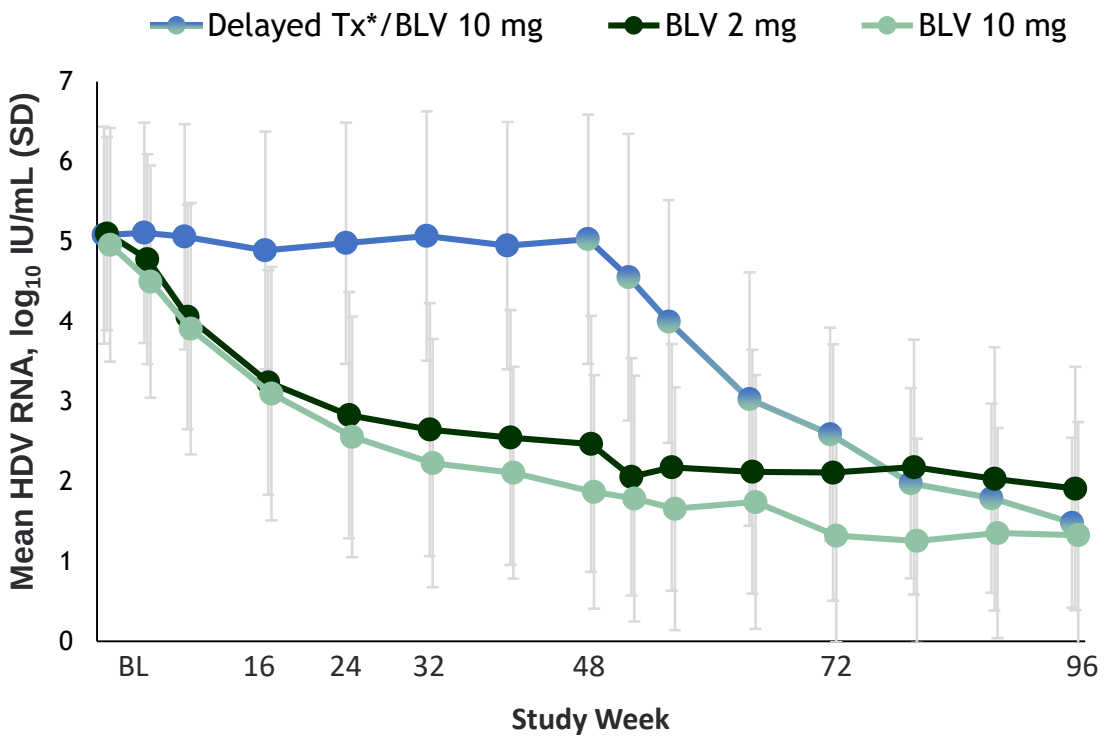
Secondary endpoints:

- 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 [RNA defined as <LLOQ (50 IU/mL) or target not detected] at Week 48

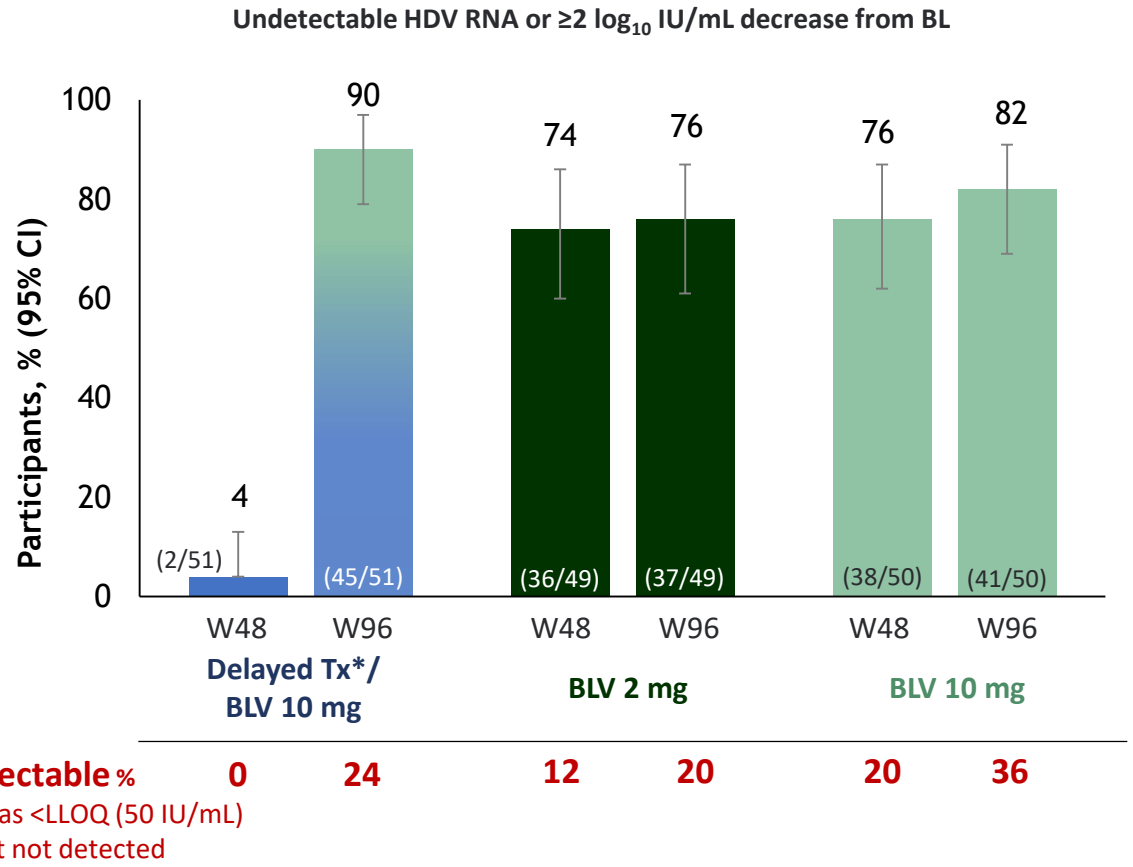
Wedemeyer H, et al. EASL 2023. Oral #OS-068

Virologic Response Through 96 Weeks

HDV RNA Decline Over Time



Virologic Response



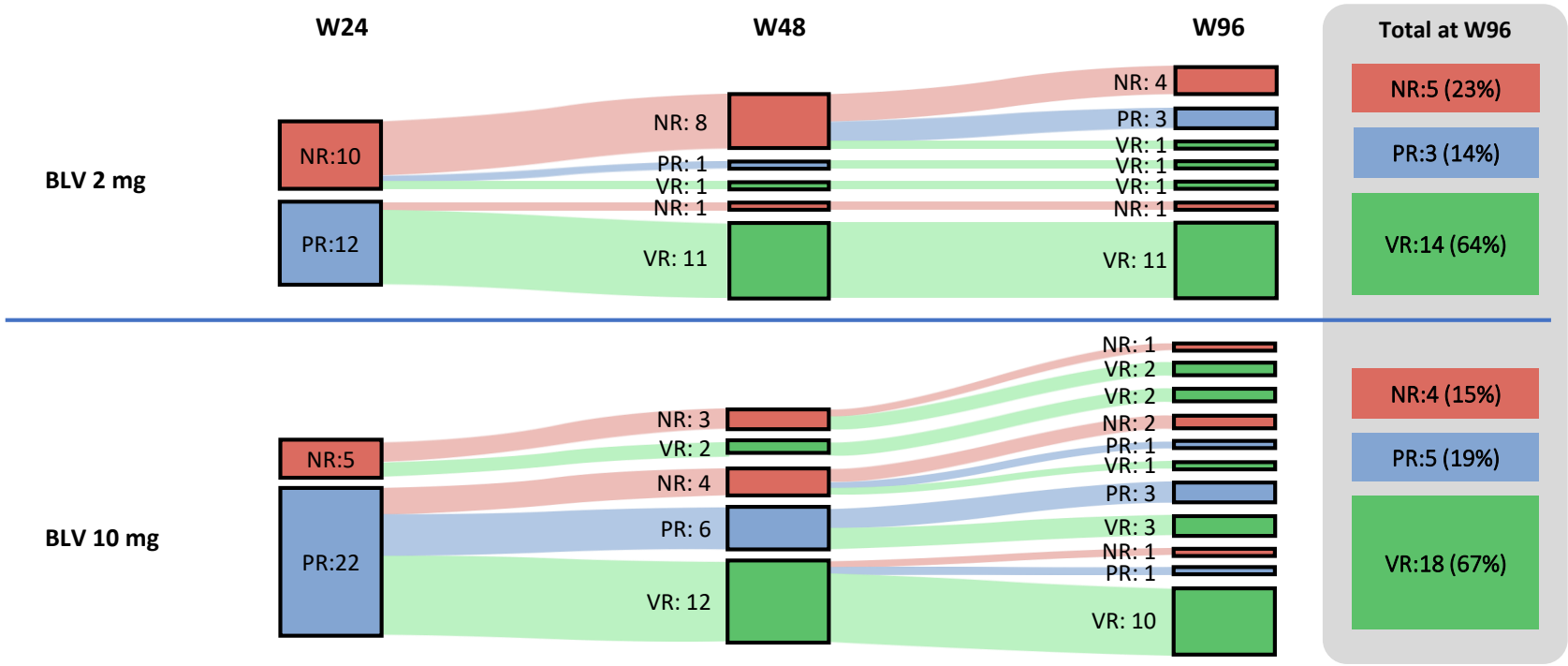
Undetectable %	Delayed Tx*/ BLV 10 mg		BLV 2 mg		BLV 10 mg	
	W48	W96	W48	W96	W48	W96
	0	24	12	20	20	36

defined as <LLOQ (50 IU/mL) or target not detected

HDV RNA decline and virologic response improved with longer term BLV therapy

Wedemeyer H, et al. EASL 2023. Oral #OS-068

Treatment Responses Improved in Suboptimal Responders at W24



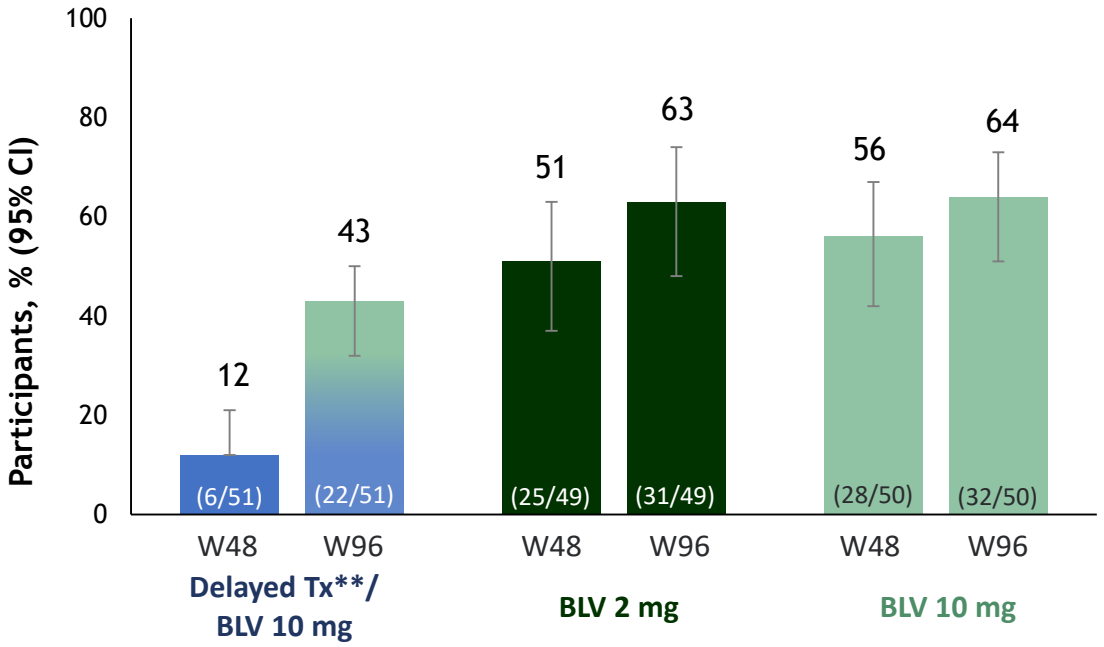
- **Non-responder (NR):** HDV RNA decrease <1 $\log_{10}$ IU/mL from BL
- **Partial responder (PR):** HDV RNA decrease ≥1 and <2 $\log_{10}$ IU/mL from BL
- **Virologic responder (VR):** HDV RNA decrease ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA

64% (BLV 2 mg) and 67% (BLV 10 mg) of W24 suboptimal responders became VRs at W96

Lampertico P, AASLD 2023

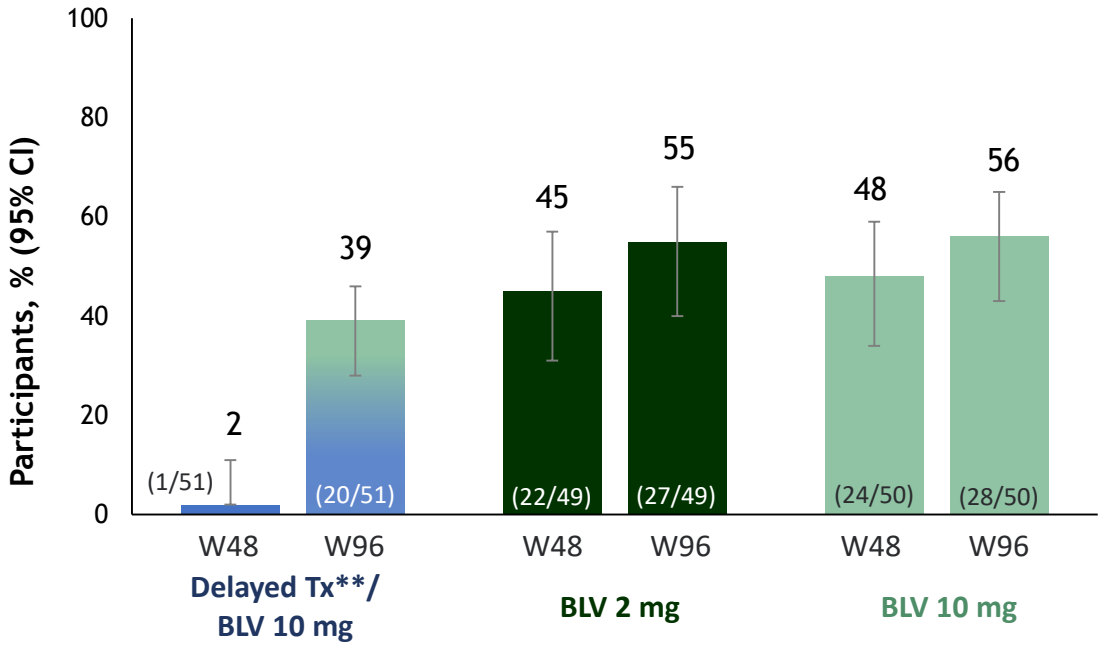
ALT and Combined Response Through 96 Weeks

ALT Normalization



Combined Response

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



ALT normalization and combined response rates improved with long term BLV therapy

Wedemeyer H, et al. EASL 2023. Oral #OS-068

The NEW ENGLAND JOURNAL of MEDICINE

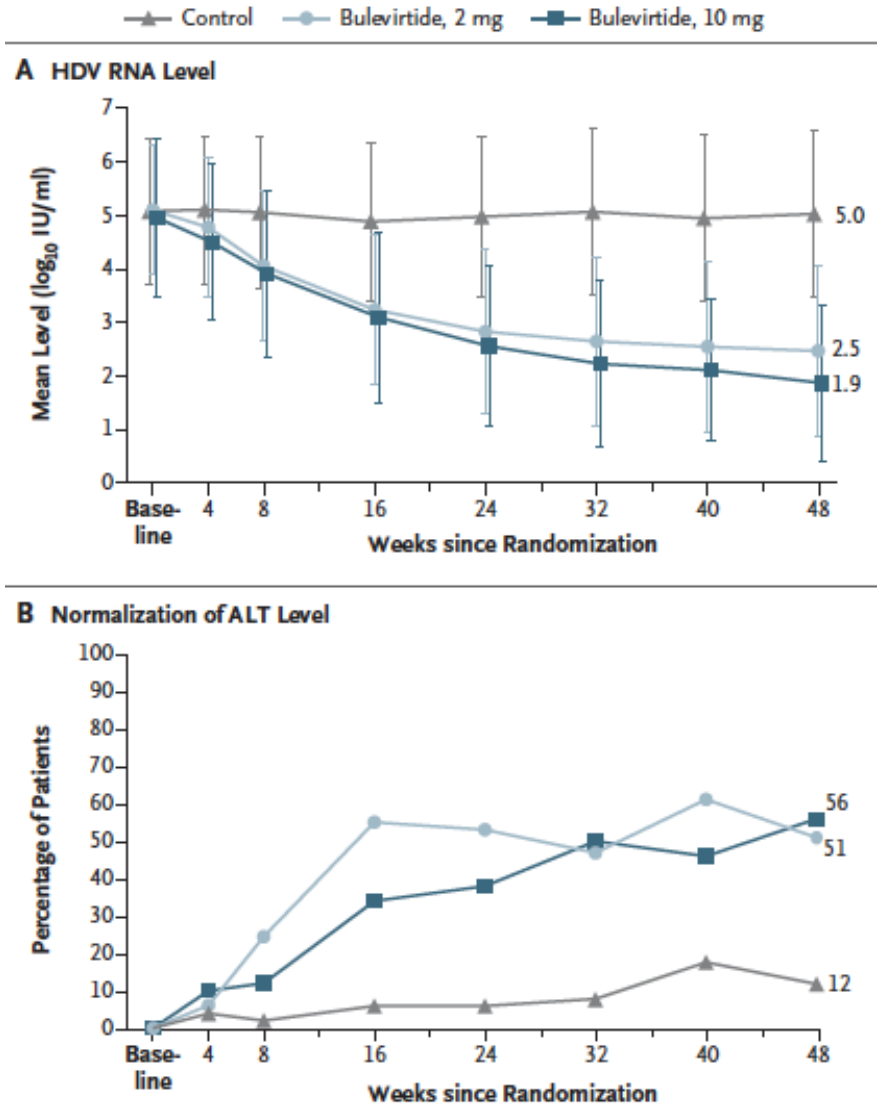
ORIGINAL ARTICLE

A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

H. Wedemeyer, S. Aleman, M.R. Brunetto, A. Blank, P. Andreone, P. Bogomolov, V. Chulanov, N. Mamonova, N. Geyvandova, V. Morozov, O. Sagalova, T. Stepanova, A. Berger, D. Manuilov, V. Suri, Q. An, B. Da, J. Flaherty, A. Osinusi, Y. Liu, U. Merle, J.S.. Wiesch, S. Zeuzem, S. Ciesek, M. Cornberg, and P. Lampertico, for the MYR 301 Study Group*

- ✓ Among patients with a combined response, normalization of the **ALT level occurred in most patients by week 24**, whereas the **HDV RNA level continued to decline between week 24 and week 48**.
- ✓ The **detailed mechanisms associated with this difference in response kinetics remain to be investigated**, including the potential effects of bile acids on immune responses and intrahepatic inflammation.

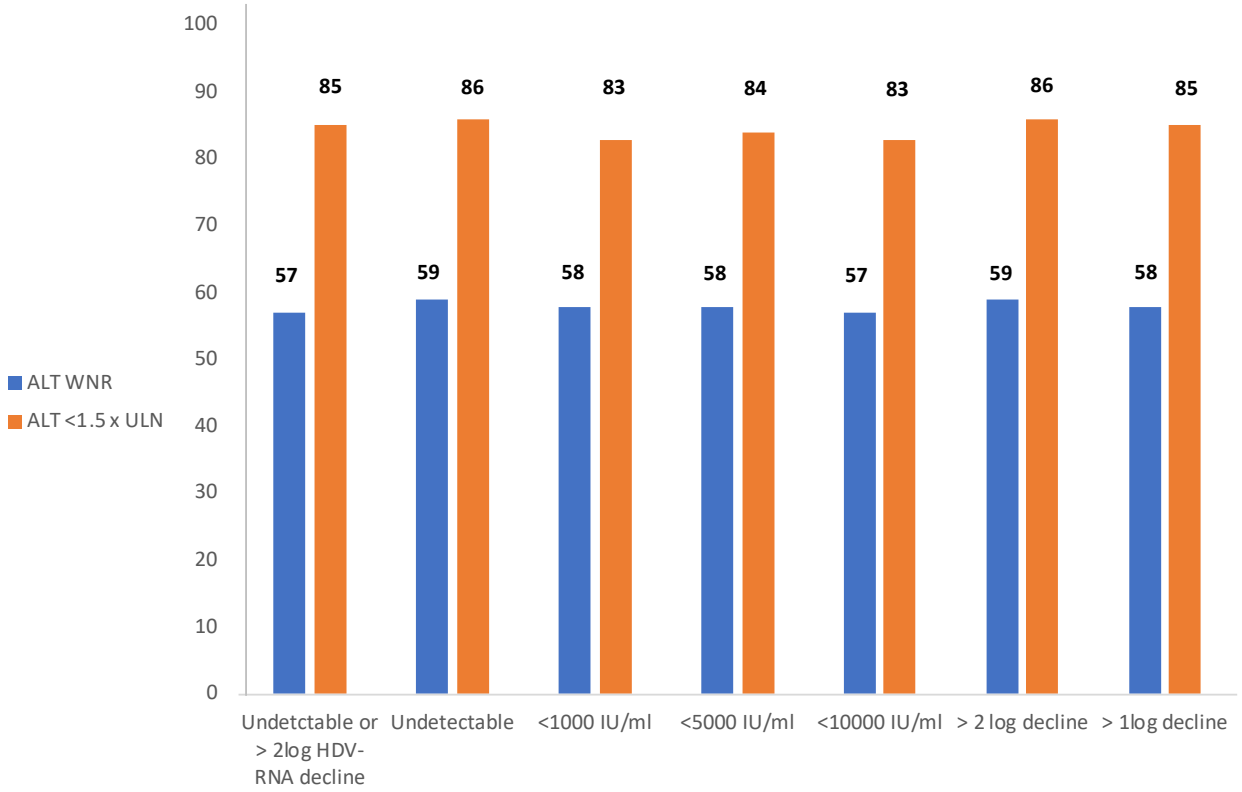
HDV-RNA kinetics and ALT normalization



Relationship Between ALT Normalization Rates and Different Virologic Response Criteria in Chronic HDV Patients Treated With Bulevirtide Monotherapy

A pooled analysis using data from **229 patients** with CHD treated with BLV 2 mg or 10 mg monotherapy for **48 weeks in 3 clinical trials** was performed: the Phase 2 MYR203 (NCT02888106) and MYR204 (NCT03852433), and the Phase 3 MYR301 (NCT03852719) studies

Biochemical response according to virologic response cut-offs at Week 48 (N:229)

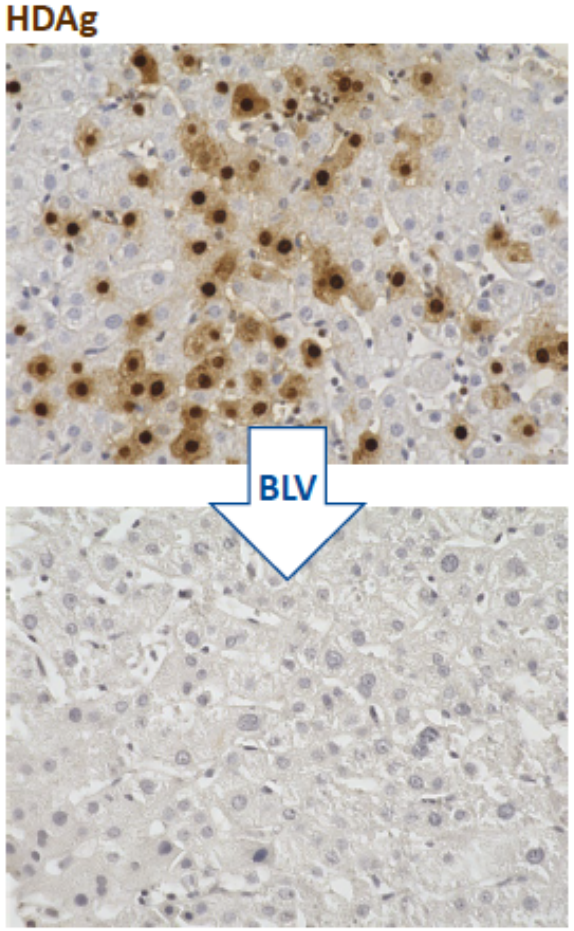


	Undetctable or > 2log HDV-RNA decline	Undetectable	<1000 IU/ml	<5000 IU/ml	<10000 IU/ml	> 2 log decline	> 1log decline
Virological Response	**79%** 180/229	**18%** 42/229	**71%** 163/229	**80%** 184/229	**85%** 94/229	**76%** 174/229	**87%** 200/229

- Viral response rates as high as 87% at 48 weeks were observed when the lowest viral response threshold (HDV RNA decline of ≥1 log10 IU/mL from BL) was used
- **Most patients had biochemical improvement** (as high as 60% for ALT ≤ ULN and 86% for ALT ≤1.5 x ULN depending on criteria), **including those who only achieved a 1-2 log10 IU/mL HDV RNA decline from BL**
- Among patients who did not achieve ALT ≤ ULN despite improvement in HDV viral load with BLV therapy, 84% (16 of 19) had ALT ≤1.5 x ULN
- Improvements in ALT were consistently observed in all viral response subgroups; **those with ≥1 log10 IU/mL decline in HDV RNA from BL had similar improvements in ALT to those with undetectable HDV RNA at W48**

Lampertico P et al, AASLD 2023

Strong decline of intrahepatic HDV markers and signs of liver inflammation after 48 weeks of treatment with BLV in CHD patients: combined intrahepatic results from the clinical trails MYR203 and MYR 301



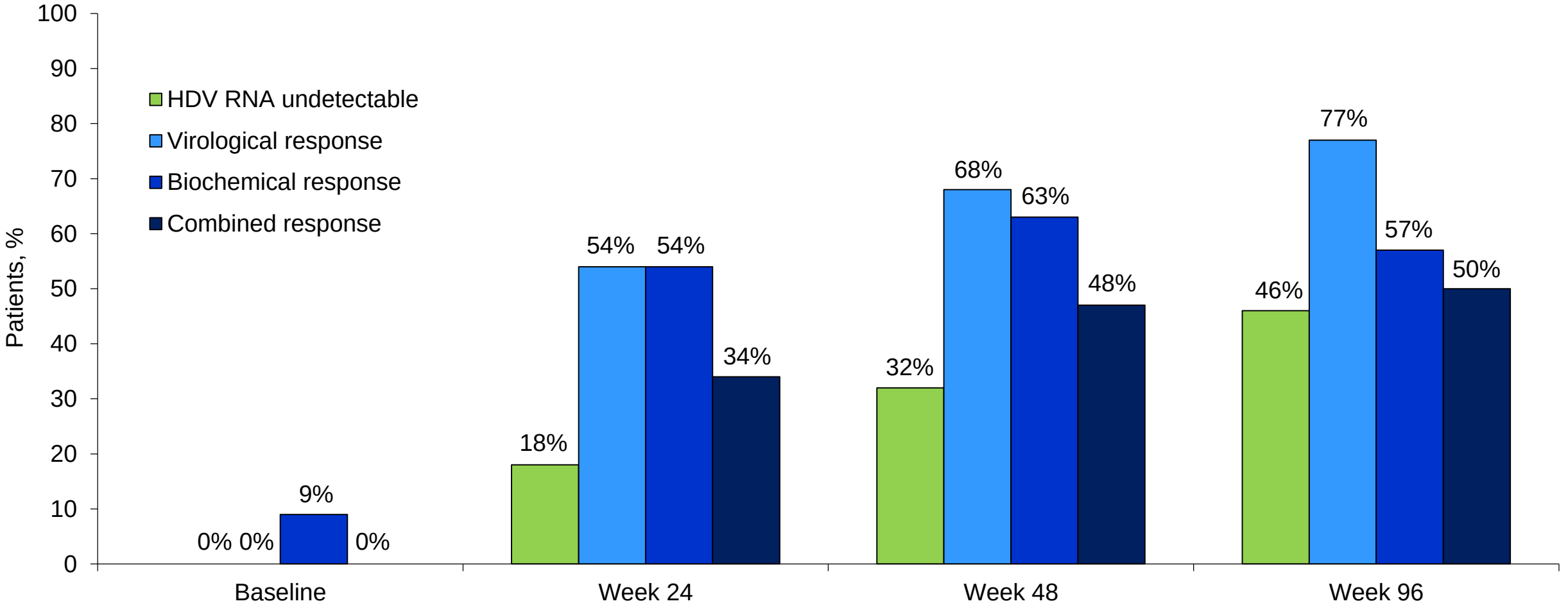
- Intrahepatic levels of HDV RNA strongly declined (>2 Log10) after 48 weeks of BLV treatment, reaching undetectable HDV RNA in 37% (2 mg) and 62% (10 mg) of patients. The results from the two trials (MYR202 and MYR203) were consistent.
- The number of HDAg+ hepatocytes strongly declined (2 Log10) reaching undetectable HDAg levels in 50% (2 mg) and 54% (10 mg) of patients.
- HDV RNA and antigen levels strongly correlated with each other indicating that the number of infected cells was reduced. This suggests that HDV relies on NTCP-dependent infection of hepatocytes for its persistence – but exact mechanism of HDV reduction still unclear!
- High levels of total HBV RNA transcripts and low pgRNA levels were indicative of a high burden of transcriptionally active HBV DNA integrations. BLV treatment did not reduce HBV DNA or RNA levels.
- Expression levels of innate immune and inflammatory genes declined in both treatment arms. Changes in host gene expression correlated with changes in HDV infection levels suggesting an improvement in liver inflammation.

- Accordingly, BLV was associated with significant reductions in liver stiffness by TE at both dose levels vs delayed treatment (-3.08 and -3.17 vs +0.88 kPa)

Allweiss L et al, Molecular biology of HBV, Paris 2022; Wedemeyer H et al, ILC 2022

SAVE-D study: Effectiveness and safety of BLV 2 mg monotherapy up to 96 weeks in a real-world compensated cirrhotic cohort

Retrospective, multicenter, European real-life BLV study (215 patients, 40 centers)



Degasperi E et al, November 2023, data on file

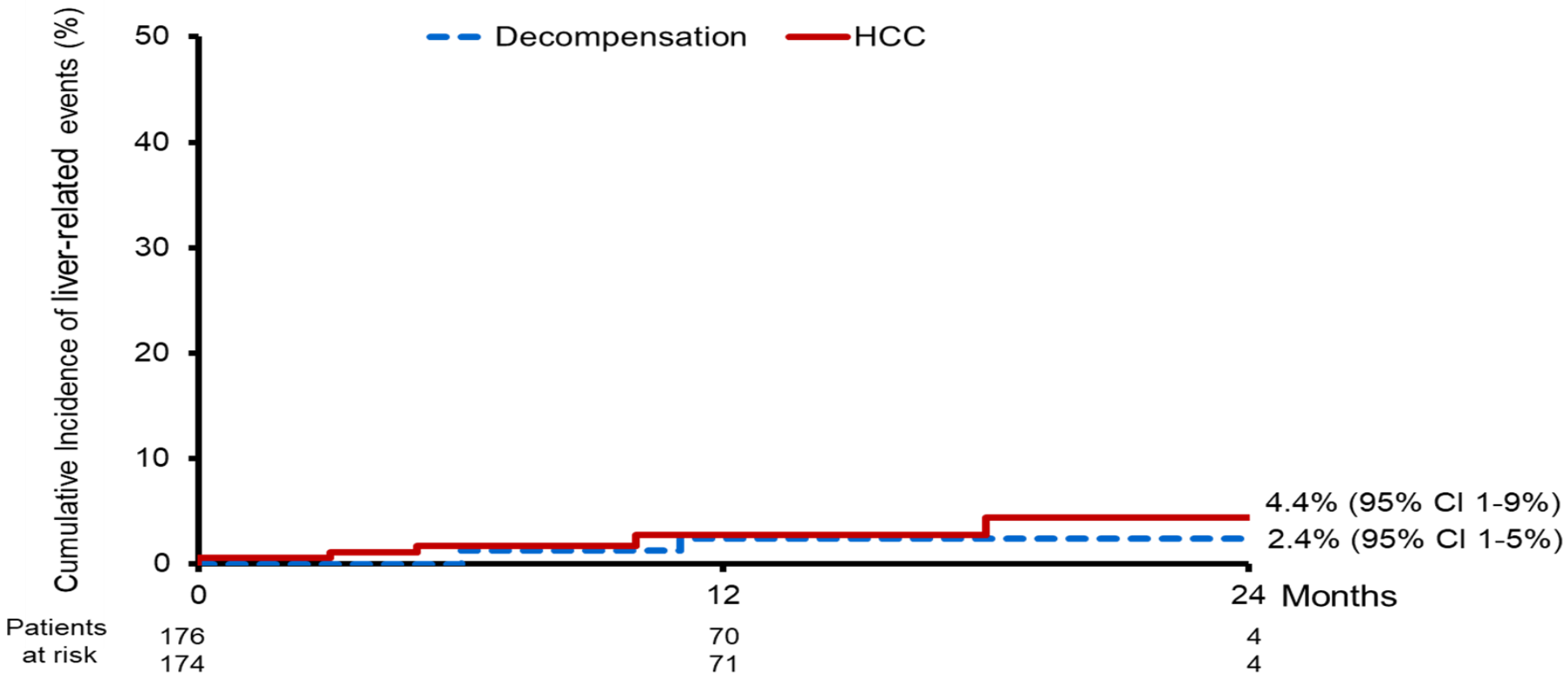
SAVE-D study: Biochemical and virological parameters during BLV treatment

Variables	Baseline	Week 24	Week 48	Week 72	Week 96	p value (A)*	p value (B)*
Bilirubin, mg/dl	1.0 (0.2-4.4)	0.8 (0.2-9.6)	0.9 (0.3-4.6)	0.7 (0.4-2.9)	0.9 (0.3-3.5)	0.28	0.46
AST, U/L	78 (7-873)	43 (11-134)	38 (21-98)	37 (18-155)	34 (20-172)	**<0.001**	**<0.001**
ALT, U/L	77 (23-1,074)	38 (12-189)	34 (14-122)	36 (6-225)	35 (10-271)	**<0.001**	**<0.001**
GGT, U/L	68 (12-583)	41 (6-237)	33 (6-184)	36 (7-236)	23 (9-131)	**<0.001**	**<0.001**
Albumin, g/dL	3.9 (2.8-4.9)	4.1 (2.2-5.3)	4.0 (2.7-5.0)	4.2 (3.2-4.8)	4.1 (3.5-4.7)	**0.01**	**0.01**
PLT, $10^3/mm^3$	89 (17-330)	88 (24-335)	90 (24-256)	90 (30-271)	99 (30-250)	0.29	**0.04**
AFP, µg/L	7 (1-596)	5 (1-116)	4 (1-15)	3 (1-40)	3 (2-7)	0.18	**<0.001**
IgG, mg/dL	2,120 (1,047-4,059)	1,743 (922-3,033)	1,776 (817-3,636)	1,610 (444-2,055)	1,622 (919-2,700)	**<0.001**	**0.003**
HBsAg, Log IU/mL	3.7 (0.8-4.5)	3.8 (0.5-4.9)	3.7 (1.5-4.8)	3.6 (1.5-4.9)	3.6 (1.9-4.2)	0.21	0.06

Degasperi E et al, Poster EASL 2023 LBP-11; Deltacure 2023 Poster #40, manuscript drafted

SAVE-D study:Clinical outcomes during long-term BLV 2mg monotherapy

2-year cumulative survival 93% (6 LT, for HCC and 2 for ESLD) (2 deaths: pneumonia; intestinal infarction, BLV-unrelated)



The yearly rates of decompensation and HCC (1.2% and 2.2% %, respectively) are encouraging when compared to the literature data untreated cohorts, where the yearly rates are 3-5%

Degasperi E et al, Poster EASL 2023 LBP-11; Deltacure 2023 Poster #40, manuscript drafted

Magritte R, Les Memoires d’un Saint 1960