18 March 2024

BLV monotherapy for CHD - PROS

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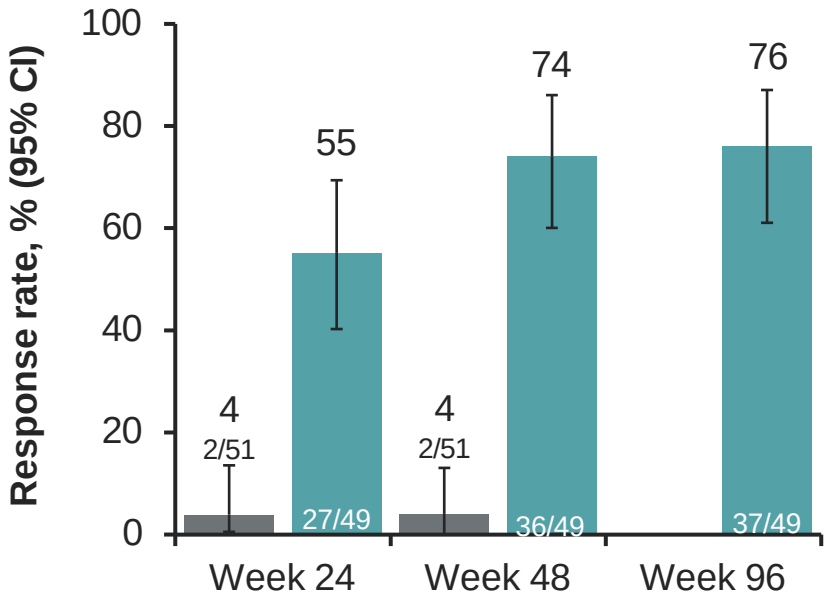
MYR301 study
BLV 2 mg monotherapy for CHD: efficacy at week 96

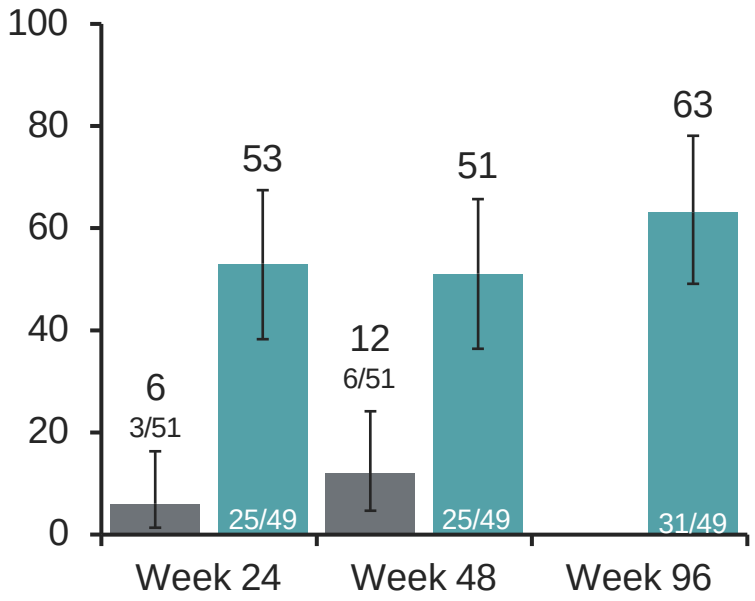
Virological response

Undetectable HDV RNA or
≥2 $\log_{10}$ IU/mL decline from BL



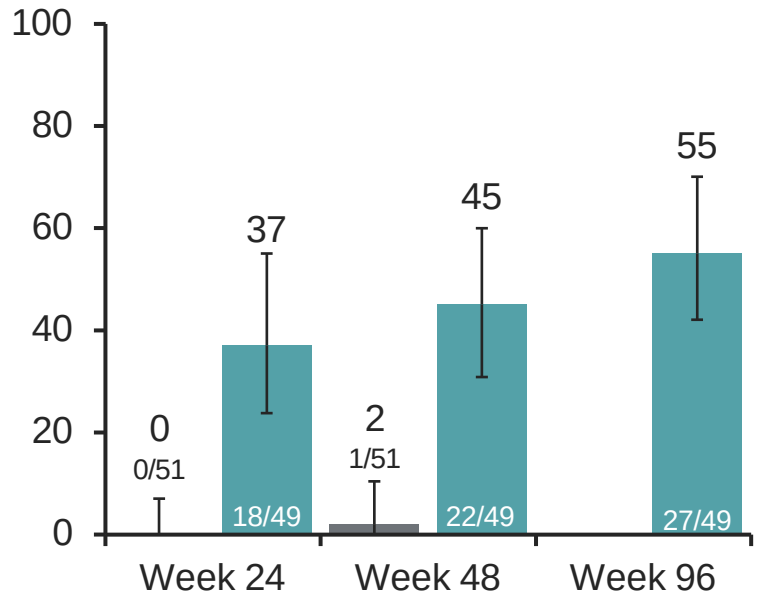
Undetectable, %	6	12	20

ALT normalisation



Combined response

Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL
decline from baseline and ALT normalisation



No treatment BLV 2 mg

BLV 2 mg led to continued virological and biochemical responses over 96 weeks

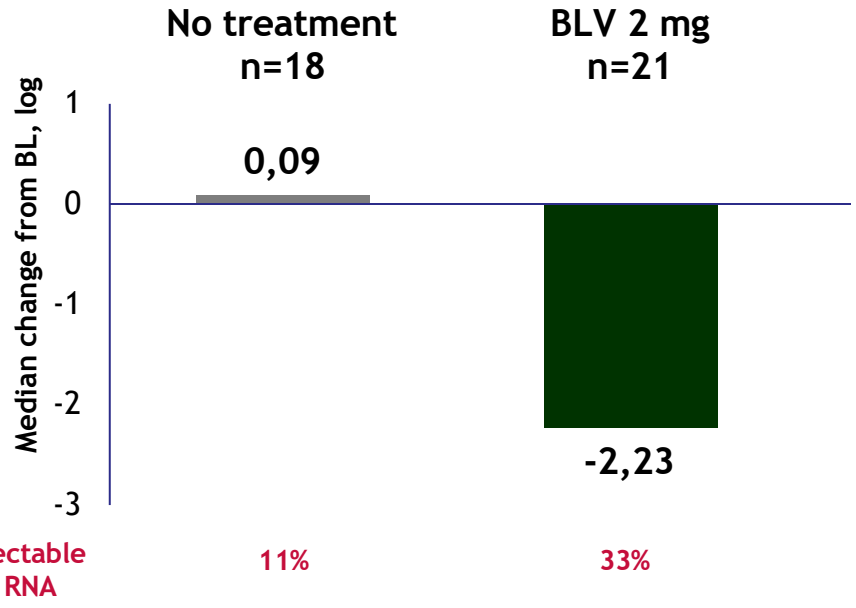
Wedemeyer H, et al. EASL ILC 2021. Oral #LBP-2730
Wedemeyer H, et al. EASL ILC 2022. Oral #GS005;
Wedemeyer H, et al. N Engl J Med 2023;389:22–32;
Wedemeyer H, et al. EASL 2023. Oral #OS-068.

Not all study arms shown. Undetectable HDV RNA defined as below lower limit of quantification (LLOQ; 50 IU/mL) (target not detected). ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). ALT normalisation 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). ALT: alanine aminotransferase; BL: baseline BLV: bulevirtide; CI: confidence interval.

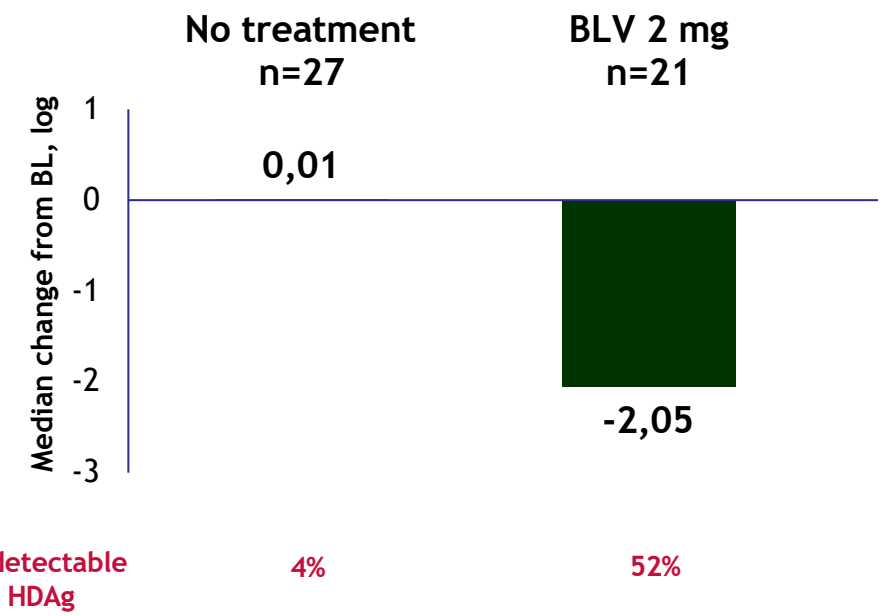
MYR301 study
Intrahepatic virological responses to BLV 2 mg monotherapy

Interim results of paired core liver biopsies from a multicenter, open-label, randomized Phase 3 study

Change in Intrahepatic HDV RNA



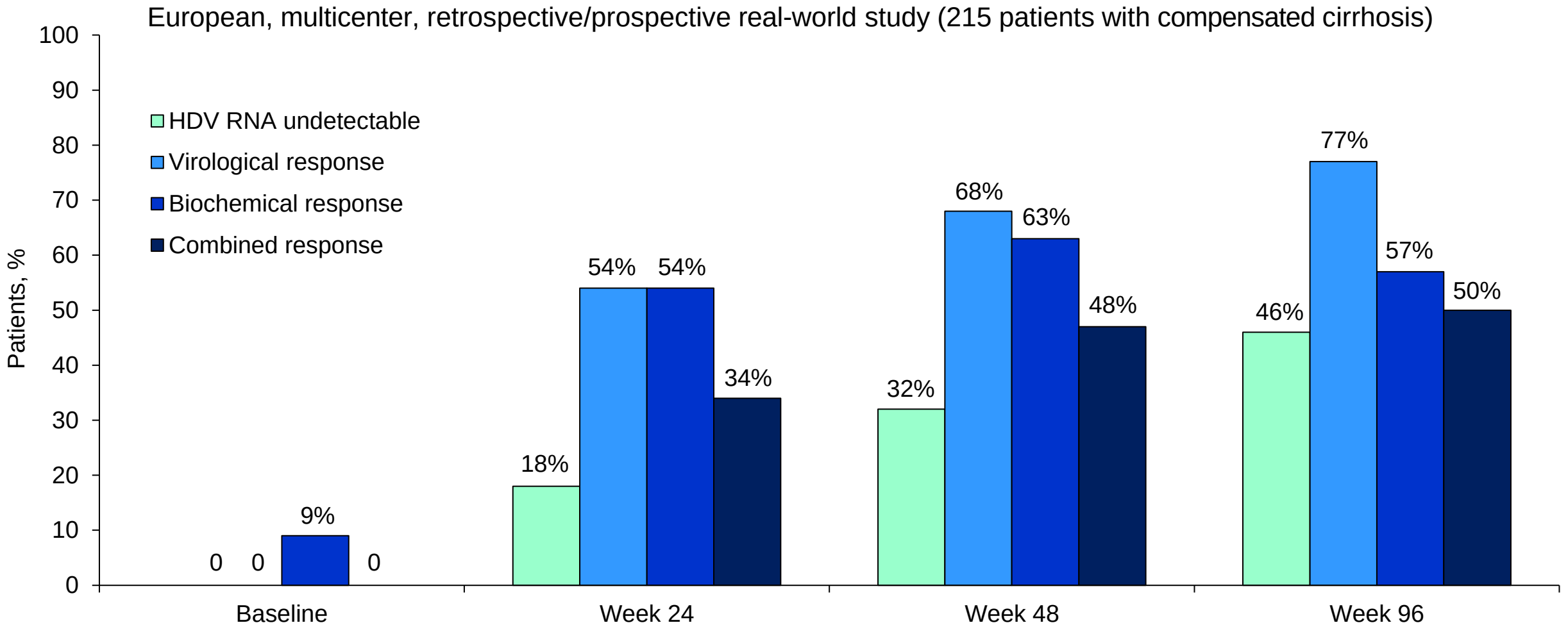
Change in HDAg+ Cells



Strong intrahepatic declines in HDV RNA and HDAg+ cells and were observed

Allweiss L, et al. AASLD 2021

SAVE-D study
Virological, biochemical responses during BLV monotherapy



HDV RNA undetectable: TND or < LOD or < LLOQ; **Virological response**: ≥2 log decline from baseline or HDV RNA TND/<LOD; **Biochemical response**: ALT <40 U/L; **Combined response**: virological and biochemical response.

Anolli MP et al, AISF meeting March 2024

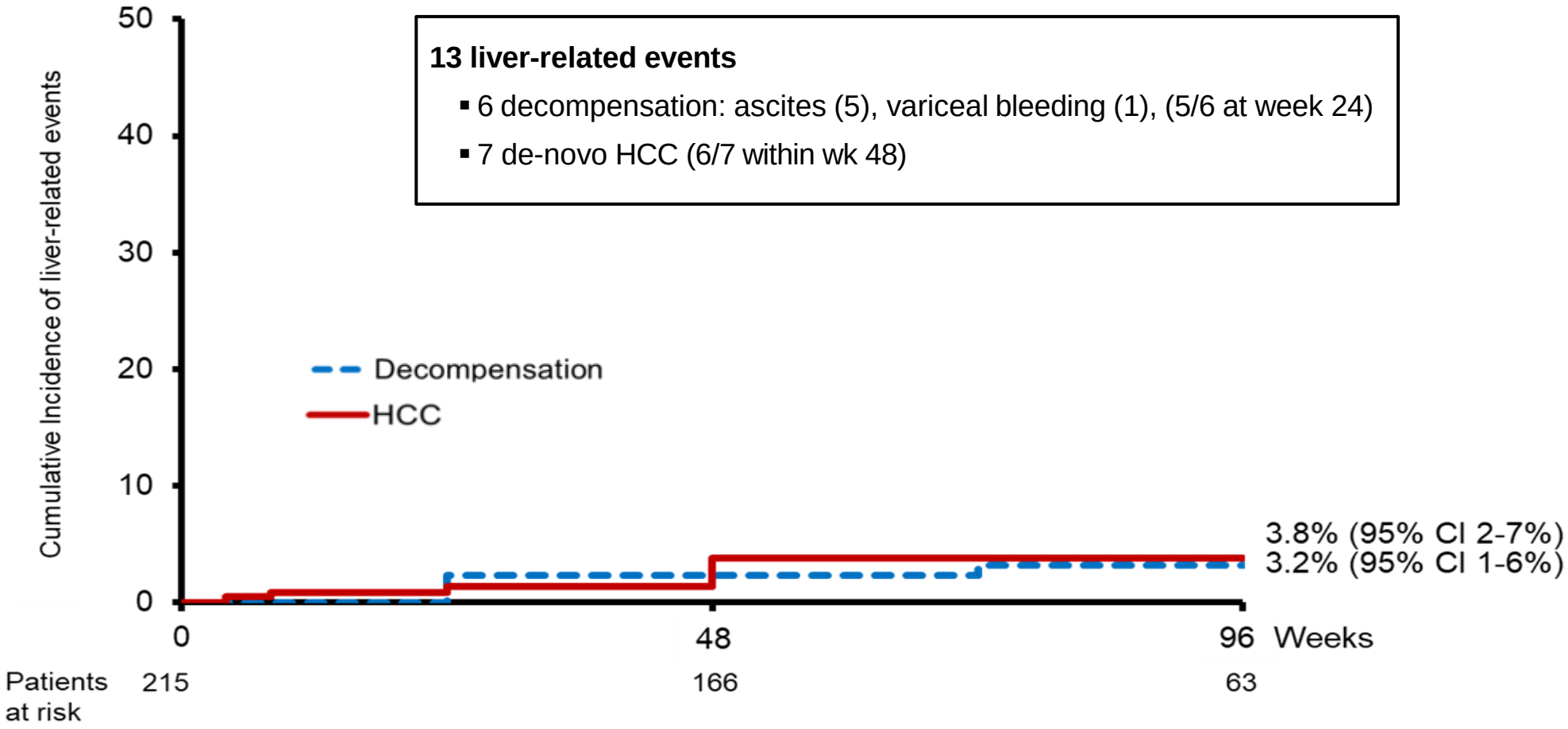
SAVE-D study
Biochemical and virological variables during BLV monotherapy

Variables	Baseline	Week 24	Week 48	Week 72	Week 96	p value (A)	p value (B)
Bilirubin, mg/dl	0.9 (0.2-4.4)	0.8 (0.3-9.6)	0.9 (0.3-4.6)	0.8 (0.2-3.6)	0.9 (0.3-3.6)	0.76	0.09
AST, U/L	79 (7-873)	43 (11-219)	39 (15-136)	35 (18-155)	36 (19-172)	**<0.001**	**<0.001**
ALT, U/L	78 (23-1,074)	39 (12-375)	34 (13-253)	36 (6-225)	36 (10-271)	**<0.001**	**<0.001**
GGT, U/L	68 (12-583)	41 (6-293)	36 (6-769)	37 (7-236)	29 (6-110)	**<0.001**	**<0.001**
Albumin, g/dL	3.9 (2.8-6.4)	4.1 (2.2-5.3)	4.1 (2.7-5.0)	4.2 (3.2-5.3)	4.1 (3.3-5.1)	**0.01**	**0.04**
PLT, 10^3/mm^3	91 (17-454)	100 (20-451)	94 (24-392)	89 (30-271)	98 (30-250)	**0.01**	0.39
Creatinine, mg/dL	0.8 (0.4-1.2)	0.8 (0.4-1.3)	0.8 (0.5-1.3)	0.8 (0.5-1.4)	0.9 (0.6-1.1)	0.14	0.26
AFP, µg/L	7 (1-596)	5 (1-35)	4 (1-22)	3 (1-40)	3 (1-7)	0.39	**<0.001**
IgG, mg/dL	2,121 (1,047-4,059)	1,721 (922-3,033)	1,705 (817-3,636)	1,613 (444-3,364)	1,598 (890-2,700)	**<0.001**	**<0.001**
HBsAg, Log IU/mL	3.7 (0.8-4.7)	3.8 (0.5-4.9)	3.6 (0.5-4.8)	3.7 (1.3-4.7)	3.6 (1.3-4.8)	0.56	0.53
LSM	18.3 (6.4-75)	15.3 (5.0-60)	14.5 (4.8-54.3)	16.5 (6.2-62.1)	14.3 (5.3-43.4)	**<0.001**	0.07
APRI	2.28 (0.2-27.7)	1.32 (0.22-7.97)	1.15 (0.30-7.77)	1.35 (0.30-6.23)	1.06 (0.33-14.9)	**<0.001**	**<0.001**
FIB-4	4.73 (0.40-27.88)	3.61 (0.56-20.75)	3.22 (0.77-14.12)	3.92 (0.74-18.27)	3.41 (0.84-25)	**<0.001**	**0.003**

(A) Subanalysis of 137 patients with complete paired data (BSL-week 48)
(B) Subanalysis of 58 patients with complete paired data (BSL-week 96)

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

European, multicenter, retrospective/prospective real-world study (215 patients with compensated cirrhosis)



Anolli MP et al, AISF meeting March 2024

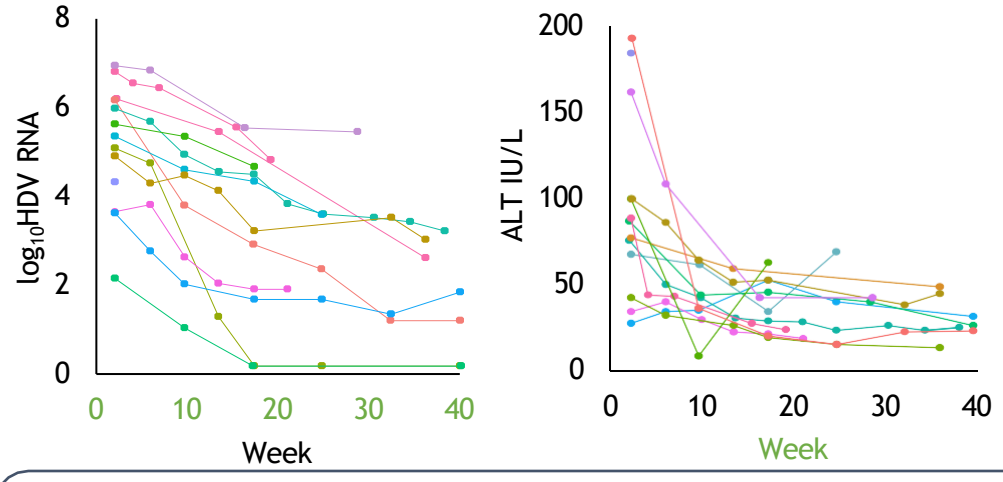
BLV monotherapy in patients with HDV-related decompensated cirrhosis (Child-B) – off-label use

Retrospective, multicenter,* real-world analysis of BLV in 15 patients with an average follow up of 23 weeks

Baseline Characteristic	Cohort (n=15)
Child-Pugh Stage, n	
A	1†
B	14
Ascites, n	10
Variceal bleeding history, n	2
Esophageal varices present, n	13
Bilirubin, µmol/L (mean ± SD)	36.1 ± 24.6
Hyperbilirubinemia (>34.2 µmol/L), n	6
Albumin, g/dL (mean ± SD)	33.0 ± 4.6
Hypoalbuminemia (<35 g/dL), n	9

Efficacy Responses

Dots and lines represent individual patients (n=13)



67% 10 of 15 patients had virologic response**

47% 7 of 15 patients had ALT normalization

27% 4 of 15 patients improved from Child-Pugh B to A

27% 4 of 15 patients had improvement of ascites

Safety profile:

- 1 patient experienced worsening of liver function after add-on pegylated IFN (not related to BLV)
- 1 patient experienced further decomposition after TIPS insertion and incarceration of hernia (not related to BLV)
- 3 patients terminated BLV therapy at liver transplantation

BLV therapy in decompensated patients led to robust virologic response, ALT normalization, and improvements in liver function

*Centers in Austria, Italy, and Germany; **HDV RNA decline of ≥2 log; †Had a history of large volume paracentesis due to ascites but resolution of ascites under ongoing diuretics at treatment initiation. Given the uncontrolled CHD, the patient was considered as decompensated following the Baveno VII recommendations. ALT, alanine aminotransferase; BLV, bulevirtide; IFN, interferon; TIPS, transjugular intrahepatic

Deterding K, et al. EASL 2023. Poster #LBP-12

SAVE-D study
Efficacy and safety of BLV monotherapy in HIV positive patients

16 HIV positive vs 199 HIV negative CHD patients

	Week 24			Week 48			Week 72			Week 96		
	HIV+	HIV-	p-value	HIV+	HIV-	p-value	HIV+	HIV-	p-value	HIV+	HIV-	p-value
Virological Response	36%	47%	0.25	80%	68%	0.58	75%	60%	0.55	67%	77%	0.67
Biochemical Response	46%	58%	0.39	80%	66%	0.53	80%	56%	0.31	100%	58%	0.10
Combined Response	21%	32%	0.43	60%	49%	0.64	75%	42%	0.21	67%	59%	0.80

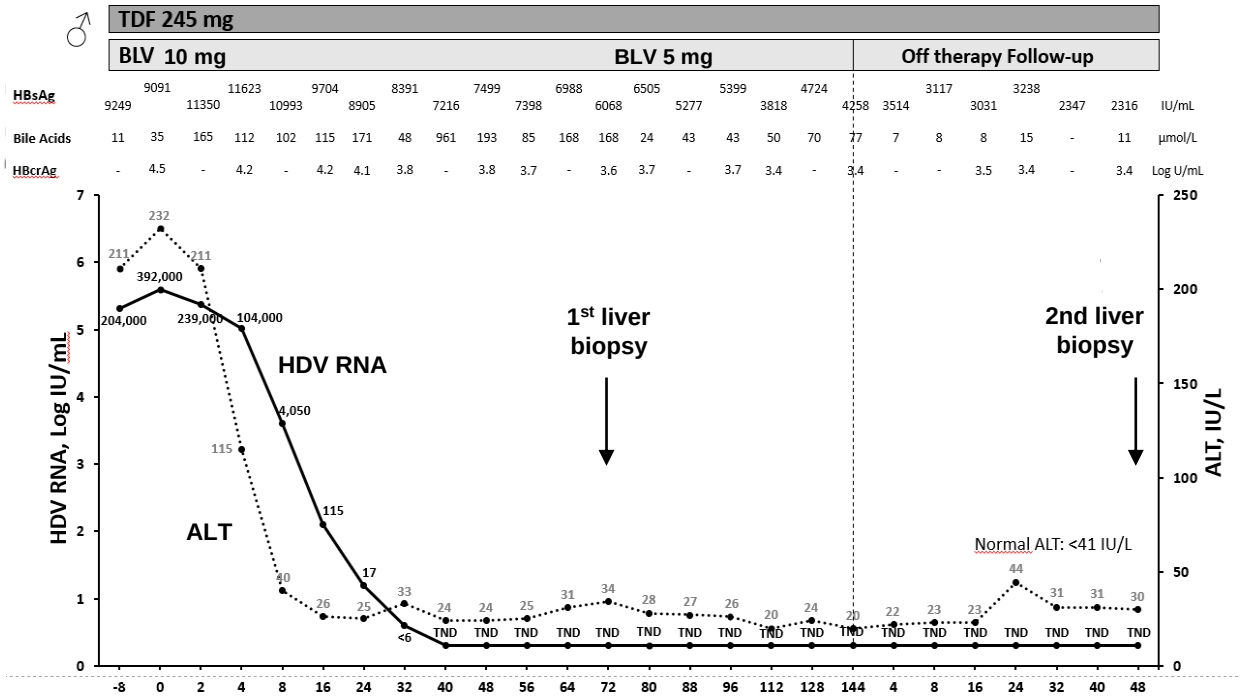
Virological response: ≥2 log decline from baseline or HDV RNA TND/<LOD; **Biochemical response**: ALT <40 U/L; **Combined response**: virological and biochemical response; comparisons were performed by Fischer exact tests

Anolli MP et al, AISF meeting March 2024

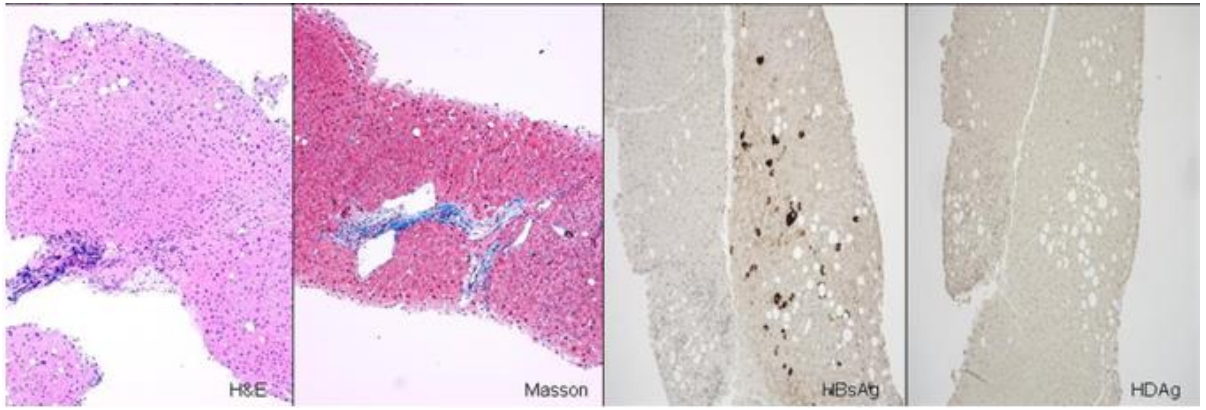
A 3-year course of BLV monotherapy may cure HDV without HBsAg loss
The "Milan patient"

A 55 year-old patient with HDV-related compensated cirrhosis with F1 esophageal varices and contraindications to pegIFNα

Virological and biochemical response during and off BLV therapy



2nd liver biopsy performed at week 48 off-therapy



H&E staining | Masson staining | HBsAg staining | HDAg staining

- Minimal features of inflammation, improvement of fibrosis (Ishak G1 S4) and resolution of autoimmunity features compared to baseline biopsy (Ishak G9 S6)
- HBsAg staining positive (<1%), HBcAg negative.
- **HDAg, HDV RNA and cccDNA undetectable (Dandri's lab)**
- **HDAg and intrahepatic HDV RNA were already undetectable** in the liver biopsy performed on-therapy at week 72 (Dandri's lab)

Clinical outcomes

- HDV suppression/cure resulted in a significant improvement in biochemistry, liver function parameters, AFP, LSM, and in regression of esophageal varices.
- No specific safety issues, BA normalized after BLV discontinuation

Conclusions

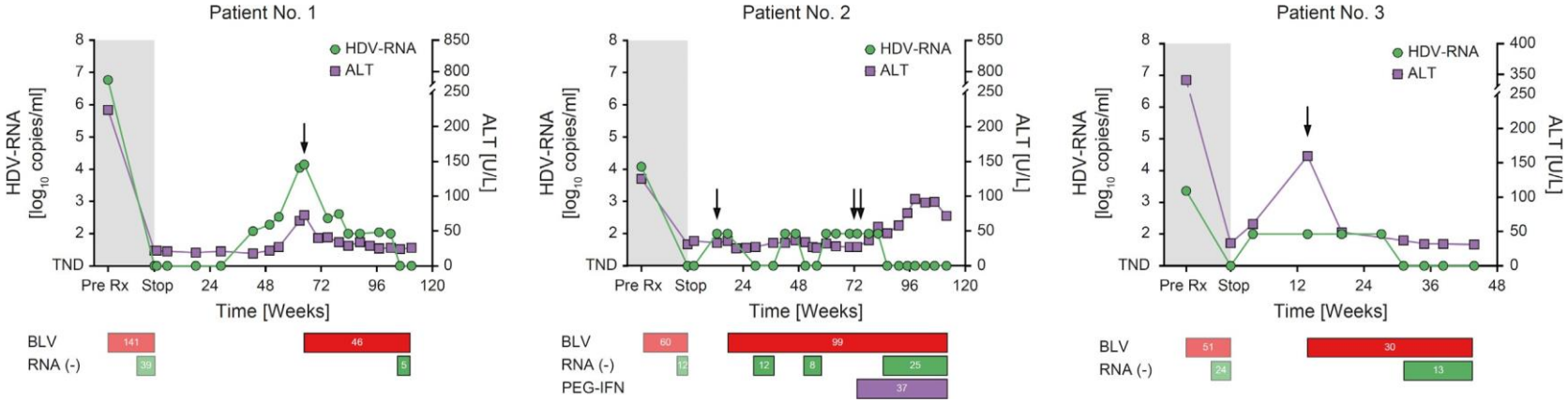
- **A 3-year course of BLV monotherapy may cure HDV infection even in difficult-to-treat patients with advanced compensated cirrhosis**
- **HDV eradication occurred without HBsAg loss**

Can we stop BLV monotherapy after 96 weeks of full viral suppression (=TND)?

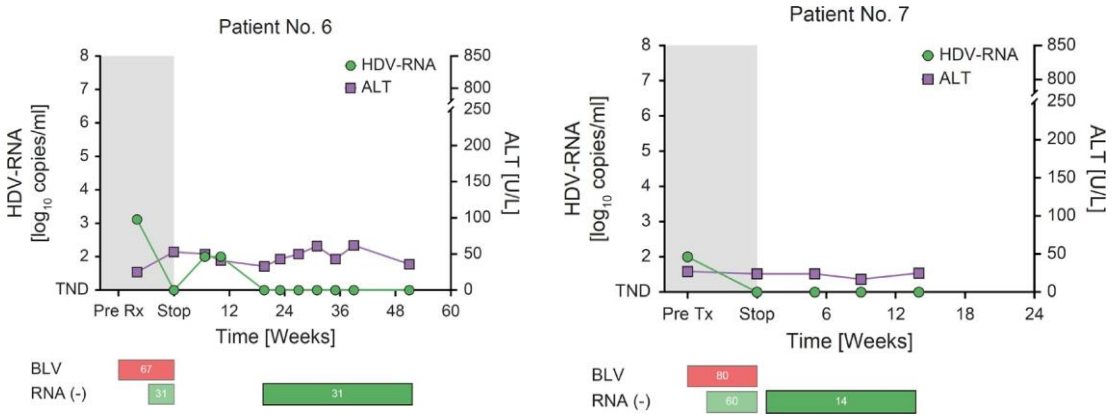
Anolli MP et al, J Hepatol 2023

The Austrian study
Discontinuation of BLV monotherapy in 5 patients with CHD

HDV Relapse after BLV STOP



HDV RNA Undetectability 24 weeks after BLV STOP



Overall 3/5 (60%) HDV relapses

n=3 HDV relapses

- #1 (F4); 39 (out of 141) weeks HDV RNA suppression
- #2 (F4); 12 (out of 60) weeks HDV RNA suppression
- #3 (F1); 24 (out of 51) weeks HDV RNA suppression

n=2 Sustained (off-tx week 24) HDV undetectability

- #6 (F4); 31 (out of 67) weeks HDV RNA suppression
- **#7 (F4); 60 (out of 80) weeks HDV RNA suppression**

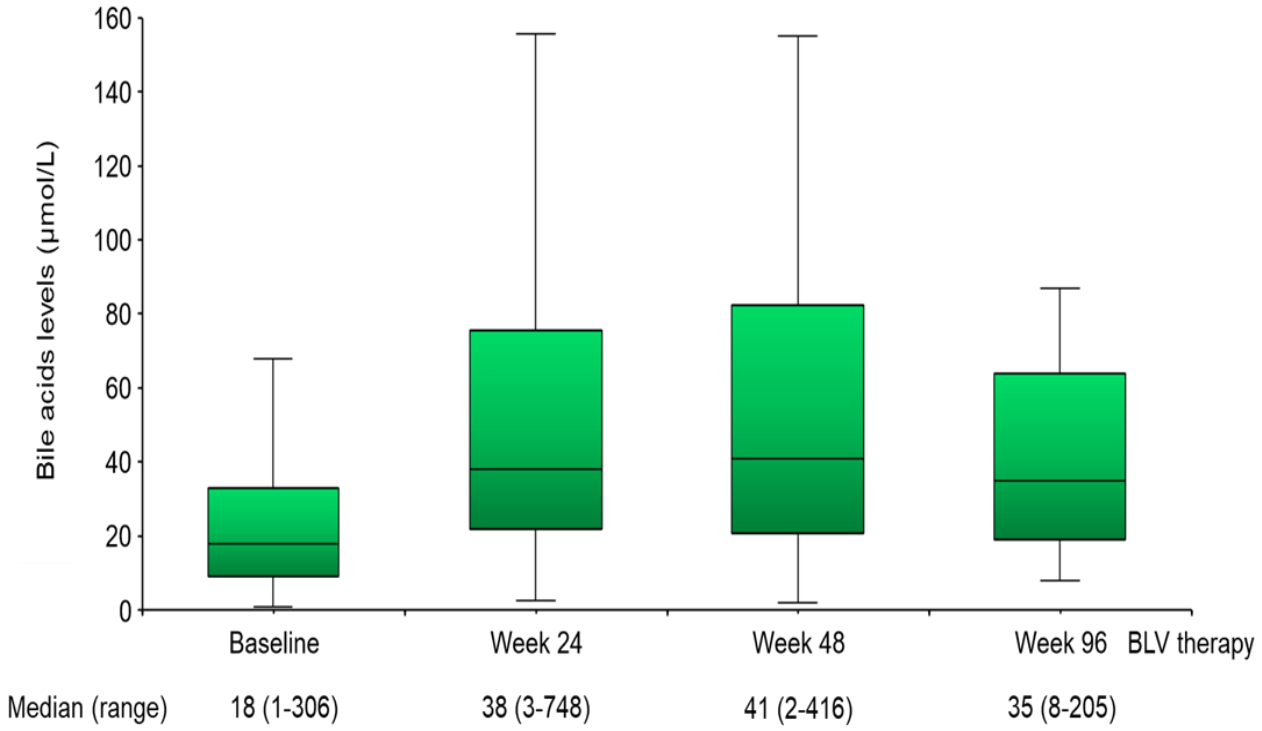
No issues following BLV re-start

Can we stop BLV monotherapy after 60 weeks of full viral suppression?

Jachs M et al, JHEP Reports 2023;5:100751

SAVE-D study
Safety and discontinuations during BLV monotherapy

European, multicenter, retrospective/prospective real-world study (215 patients with compensated cirrhosis)



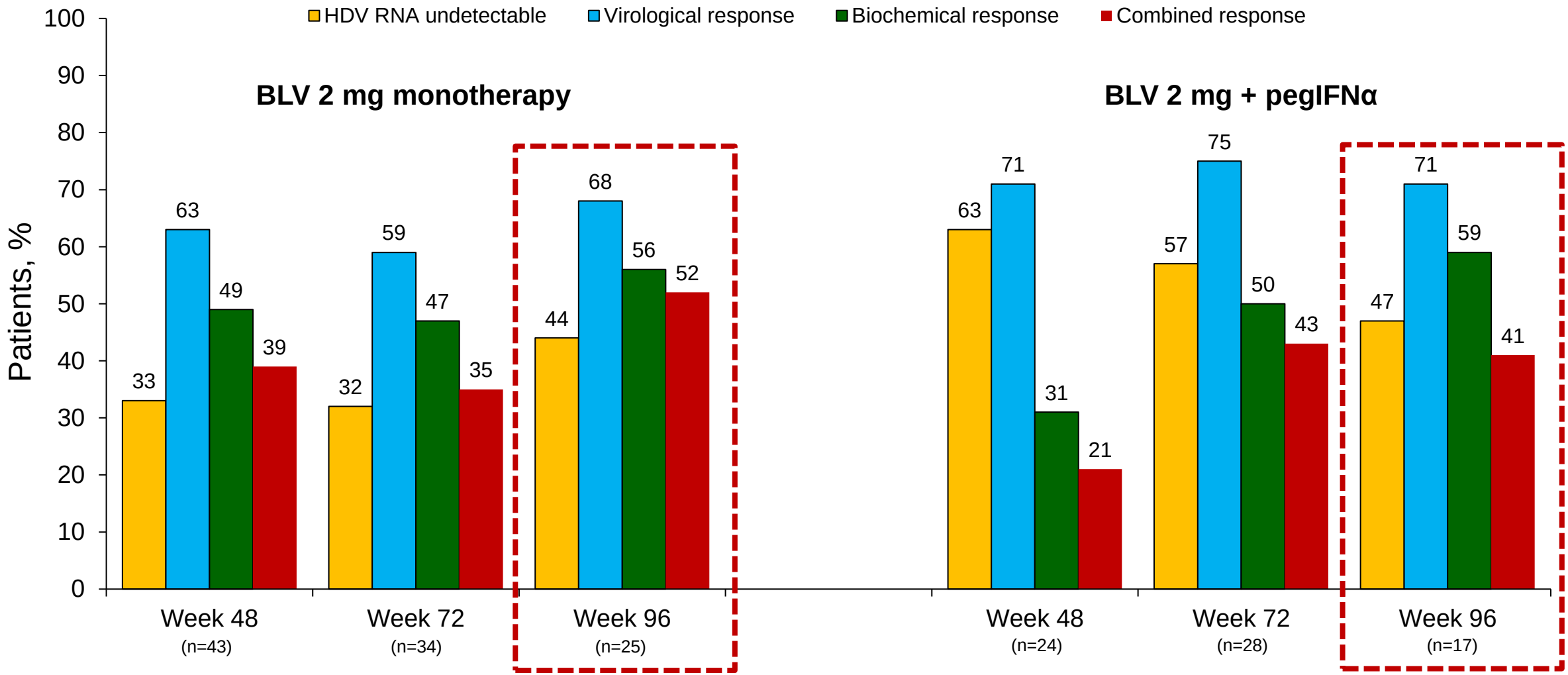
Safety events/withdrawals:

- Pruritus, mild and transient:19 (9%)
- Injection site reactions, mild and transient: 6 (3%)
- TA-SAE: 1 (0.5%)
- BLV withdrawal: 12 (5%)*
- Lost to follow-up: 7 (3%)

*n=1 grade 3 maculopapular rash; n=3 viral non-response; n=1 non-compliance; n=5 add-on IFN; n=2 long-term HDV RNA undetectable

Anolli MP et al, AISF meeting March 2024

The French ATU cohort
BLV 2 mg ± pegIFNα in patients with CHD for up to 96 weeks



Virological response: Undetectable HDV RNA or ≥2-log decline from baseline; **Biochemical response**: ALT <40 U/L; **Combined response**: virological and biochemical

de Lédinghen V et al, AASLD 2022

BLV monotherapy for HDV - Summary

- Many studies on BLV 2 mg monotherapy (phase 2 and 3, real-world studies)
- Effective independently of the liver disease severity
- Efficacy increases over time
- No significant side effects, no BLV resistance, rare DDI
- No contraindications, can be used also in patients with autoimmune disease
- Less expensive, easy monitoring, no specific expertise required
- BLV + pegIFN: very limited and contradictory efficacy data (see EASL 2024)
- And 80% of my patients cannot be treated with pegIFN

In conclusion, BLV monotherapy is the SOC treatment for CHD in 2024

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UNIVERSITÀ DEGLI STUDI DI MILANO

Thank You for Your Attention!