12 October 2023

Bulevirtide for patients with CHD
Post EASL 2023 update

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Disclosures

Advisory Board/Speaker Bureau for:

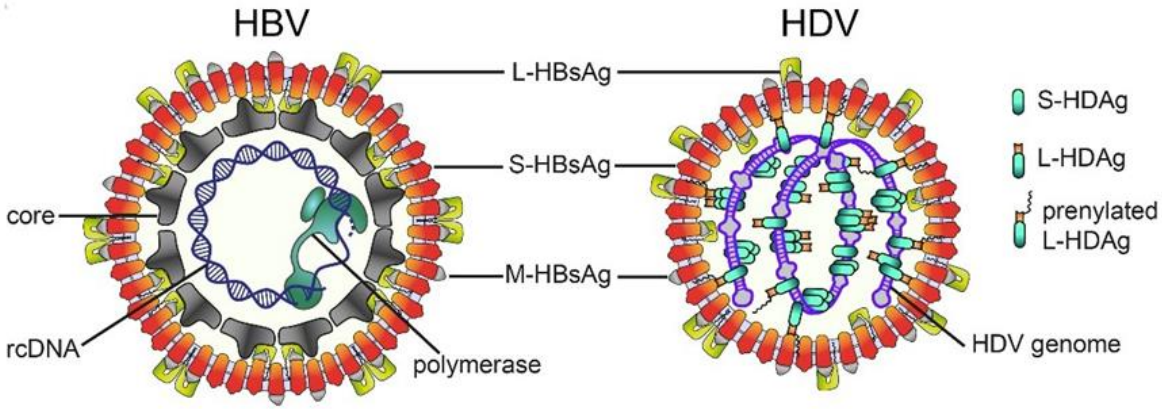
- ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANSSEN, MYR, EIGER, ANTIOS, ALIGOS, VIR, GRIFOLS, ALTONA, ROBOSCREEN

Hepatitis D (delta) Virus infection

- The «Delta agent» was discovered in 1977 by Mario Rizzetto
- Small RNA defective virus that needs HBsAg for its propagation (HBV/HDV coinfection)
- Of the ~250 million HBsAg carriers, 10-20 million are also anti-HDV positive (rare disease)
- Causes the most severe form of chronic viral hepatitis

  More rapid progression to liver cirrhosis and liver cancer; 5-7x more likely to develop cirrhosis and HCC vs HBV

- Anti-HDV therapies: NUC not effective, PegIFNα effective in only 15-20% of the patients (not EMA or FDA approved)
- New therapies are needed



Modified from Urban S, Neumann-Haefelin C, Lampertico P. GUT 2021

Goals/Endpoints of anti-HDV treatment

- Improve survival
- Reduce liver related complications (ESLD, HCC…)
- HDV RNA undetectable ± HBsAg loss/seroconversion
- Virological response (> 2 log IU/ml decline HDV RNA)
- Combined response (HDV RNA decline >2 log + ALT normalization)
- Biochemical response
- Histological response

At different time points: during therapy, EOT, EOF (≥24 weeks off therapy)

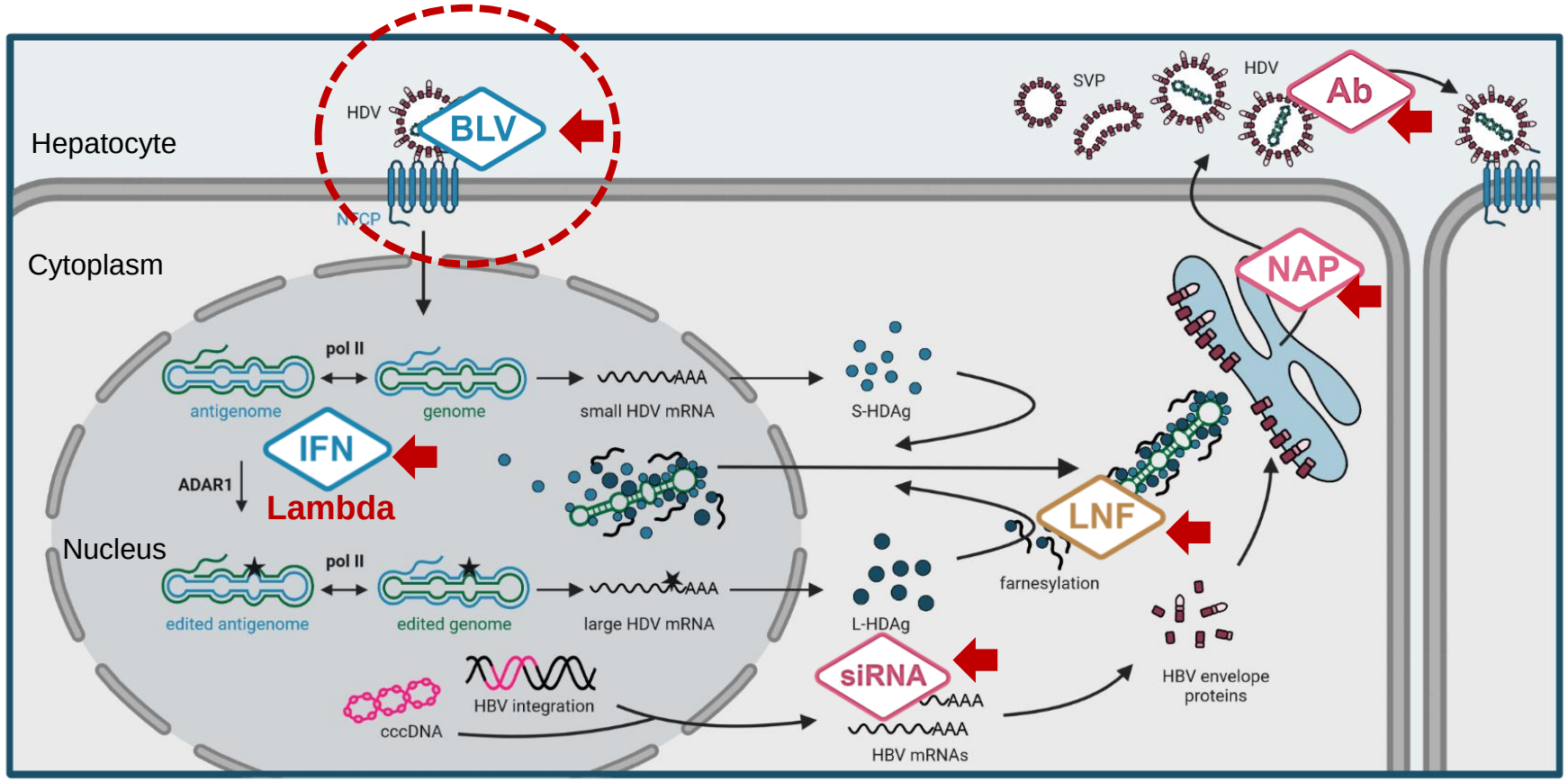
modified from Yurdaydin C et al J Hepatol 2019;70:1008-15; Cornberg M et al, J Hepatol 2020;72:539-57, Urban et al, Gut 2021

Antiviral treatment in HDV patients: possible strategies

STRATEGIES	GOAL	DURATION OF THERAPY	ENDPOINT	TIMING OF ENDPOINT
Short-term (finite) therapy	Cure	≤48 weeks	**Preferred:** HBsAg loss + HDV RNA <LLoQ **Alternate:** HDV RNA <LLoQ	Off-therapy (24 weeks)
Long-term therapy	Control	>48 weeks	**Preferred**: HDV RNA <LLoQ **Alternate***: HDV RNA >2 log decline + ALT normalization	On-therapy (48 weeks)

***FDA Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry (Oct 2019)**
"…….in certain situations, such as for drugs that are intended to be used as chronic suppressive therapy, a greater than or equal to 2 log10 decline in HDV RNA and ALT normalization on-treatment could be considered an acceptable surrogate endpoint reasonably likely to predict clinical benefit"

Therapeutic targets for HDV infection

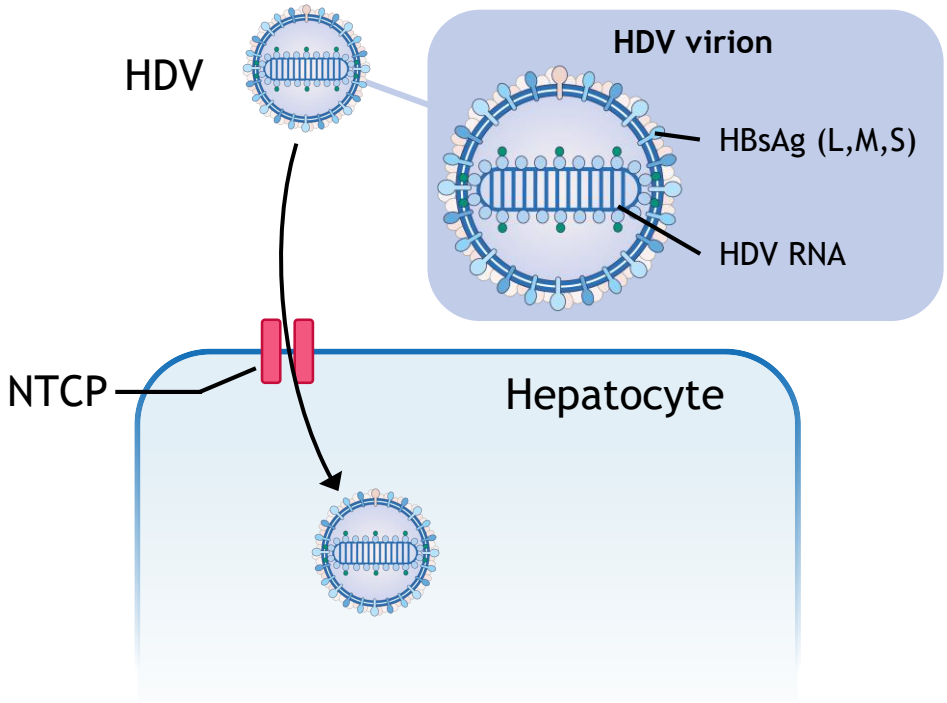


NUC therapy for HBV does not directly interfere with HDV replication

Courtesy of L. Allweiss/A. Volmari, adapted from Dandri et al J. Hepatol 2022

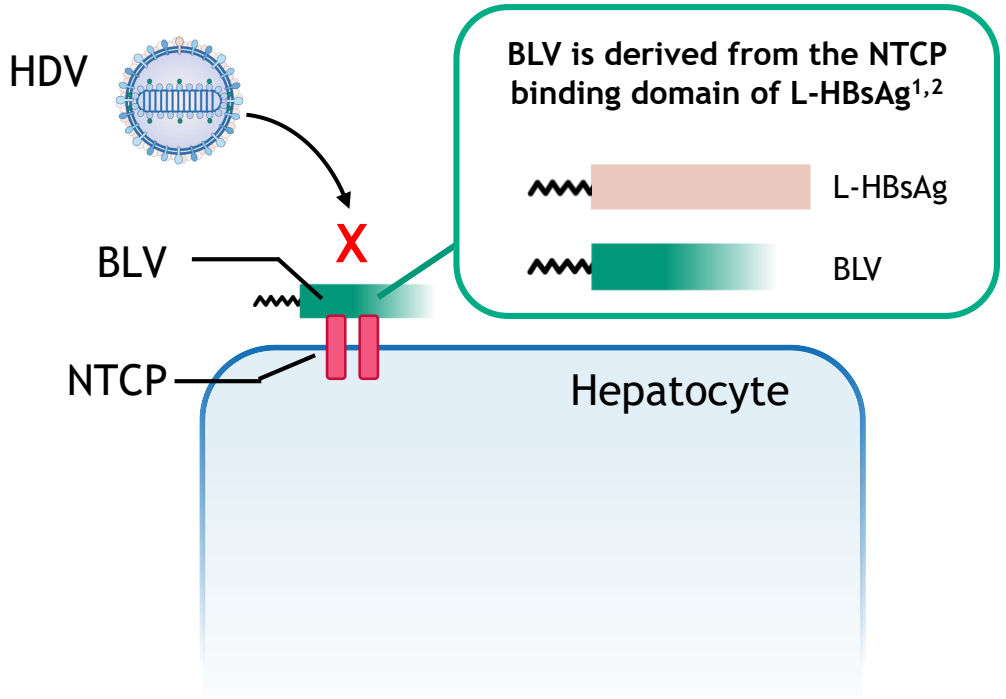
Bulevirtide (BLV) is an HDV entry inhibitor (2 mg/day sc injection)

HDV infects hepatocytes via the NTCP bile acid transporter[1]



Adapted from Zhang Z, Urban S. J Hepatol 2021;74:686-99

BLV binds to NTCP preventing entry of HDV into hepatocytes[2,3]



Adapted from Zhang Z, Urban S. J Hepatol 2021;74:686-99

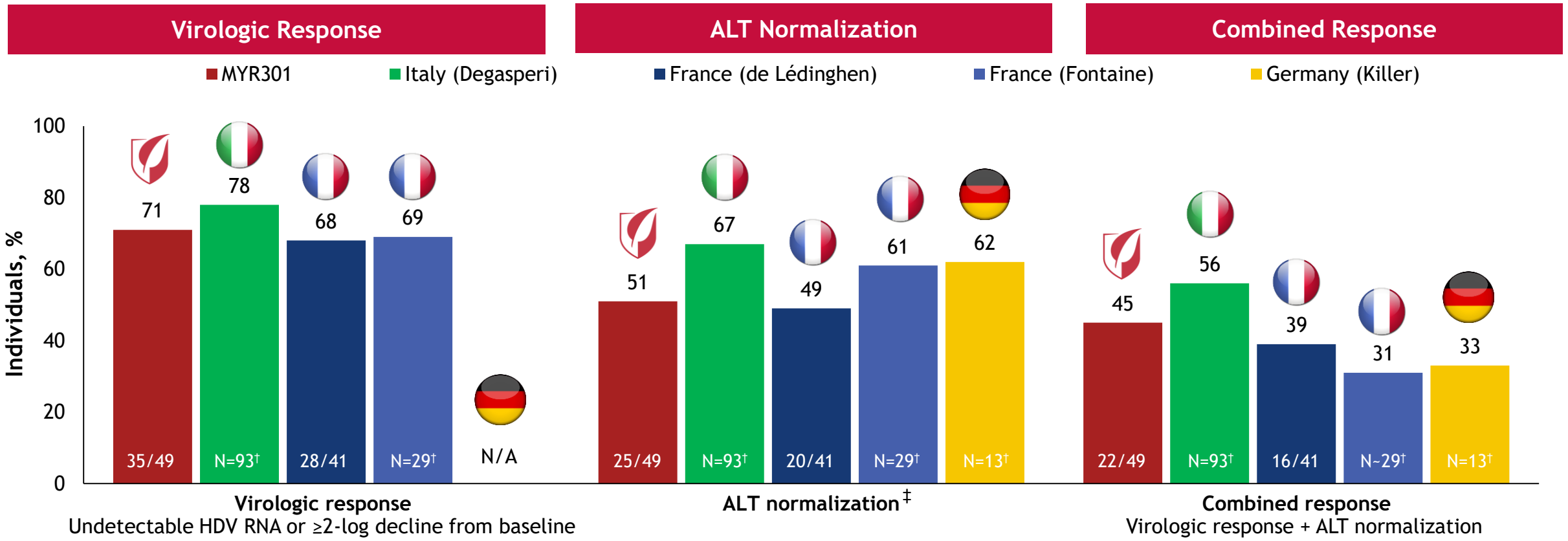
BLV is a specific inhibitor of the NTCP bile acid transporter, the entry receptor for HDV[2]

1. Zhang Z, Urban S. J Hepatol 2021;74:686-99; 2. Kang C, Syed YY. Drugs 2020;8
3. EMC. HEPCLUDEX ▼ (bulevirtide) Additional monitoring SmPC. Available at: https://www.medicines.org.uk/emc/product/13482 (accessed July 2023).

BLV does not directly inhibit HDV replication in infected cells!

BLV 2 mg monotherapy in CHD: efficacy at week 48 MYR301 and RWD Sets

*NOT HEAD-TO-HEAD COMPARISONS



Week 48 RWD support the efficacy of BLV 2 mg observed in MYR301

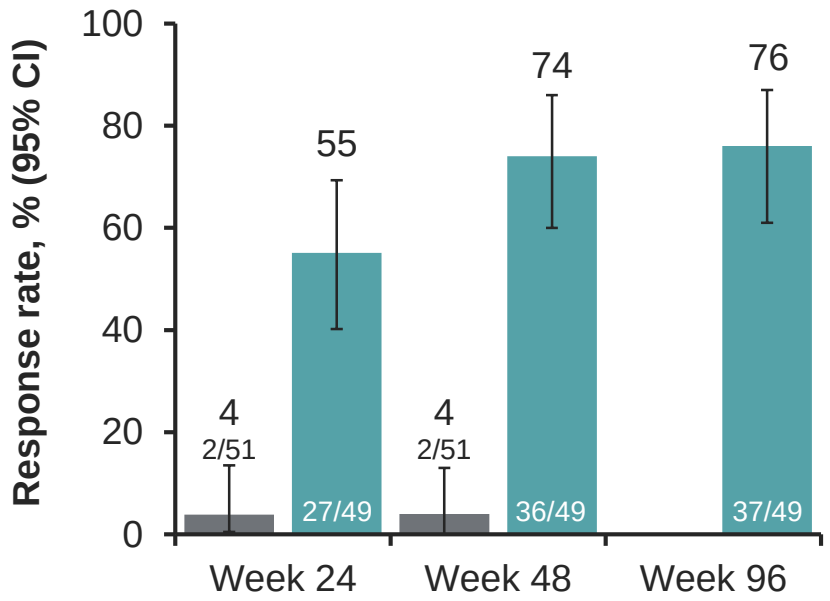
*NOT HEAD-TO-HEAD COMPARISONS. This graphic serves to illustrate outcomes obtained from different studies, which are therefore not directly comparable as study populations are NOT matched

1. Wedemeyer H, et al. NEJM 2023; 2. Degasperi A, et al. AASLD 2022. Oral #5013; 3. de Lédinghen V, et al. AASLD 2021. Oral #21; 4. Fontaine H, et al. EASL 2022. Oral #OS093; 5. Killer A, et al. EASL 2022. Poster #SAT345

MYR301: efficacy at Week 96

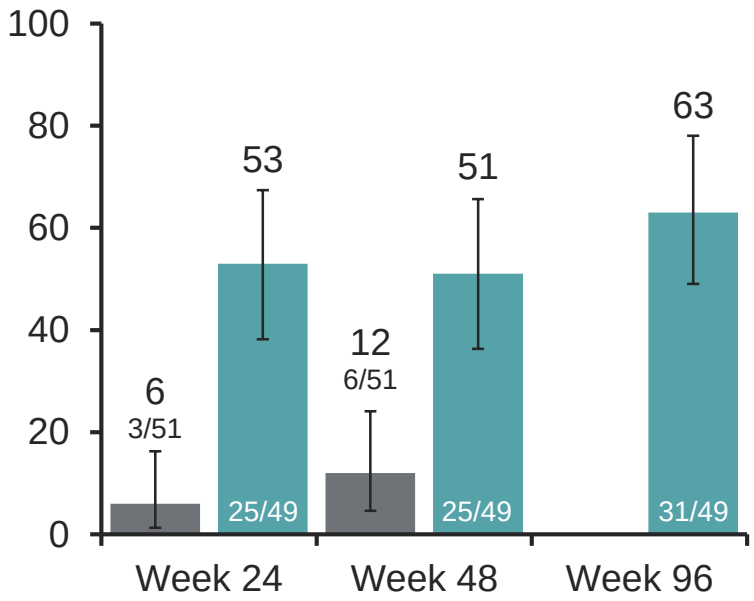
Virological response

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



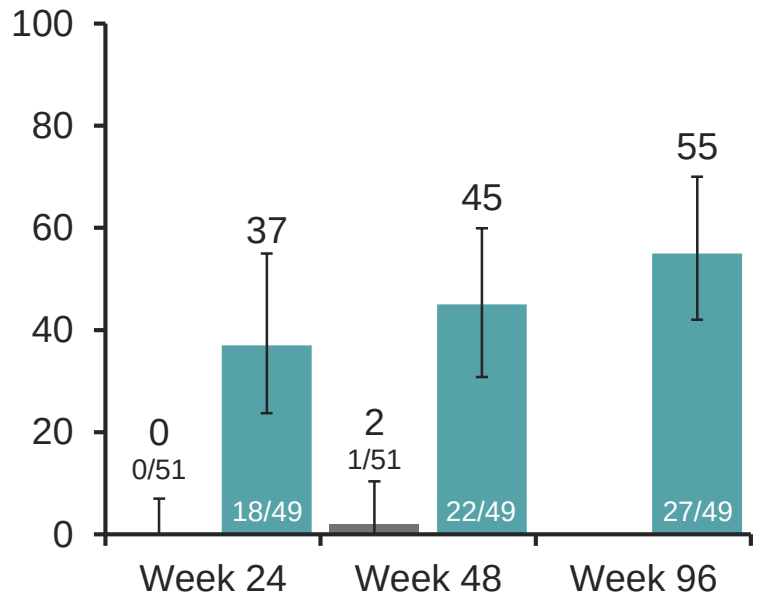
Undetectable, %	6	12	20

ALT normalisation



Combined response

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



No treatment BLV 2 mg

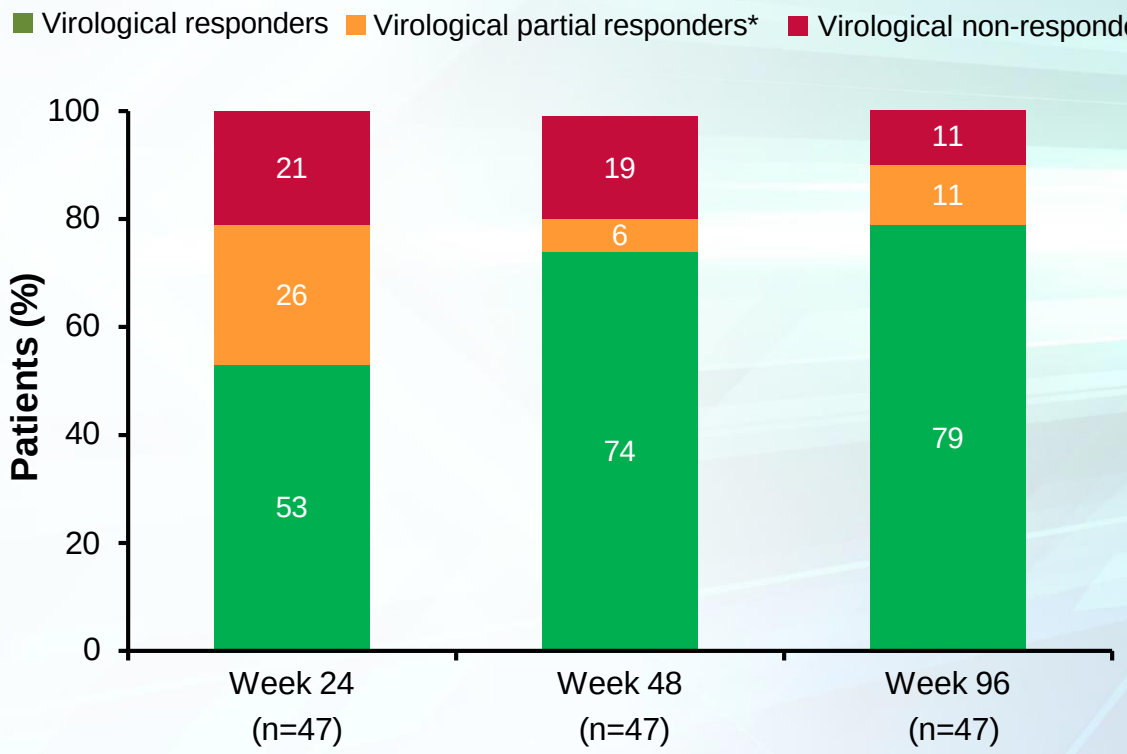
BLV 2 mg led to continued virological and biochemical responses over 96 weeks

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
Efficacy improvements with BLV monotherapy through Week 96 in early suboptimal responders

Change in virological response category from Week 24 to Week 96 with BLV 2 mg



Efficacy responses

92% 11/12 virological partial responders at Week 24 became virological responders at Week 96

30% 3/10 virological non-responders at Week 24 became virological responders at Week 96

83%‡ 5/6 patients who remained virological non-responders achieved ALT declines of >50% from BL at Week 96

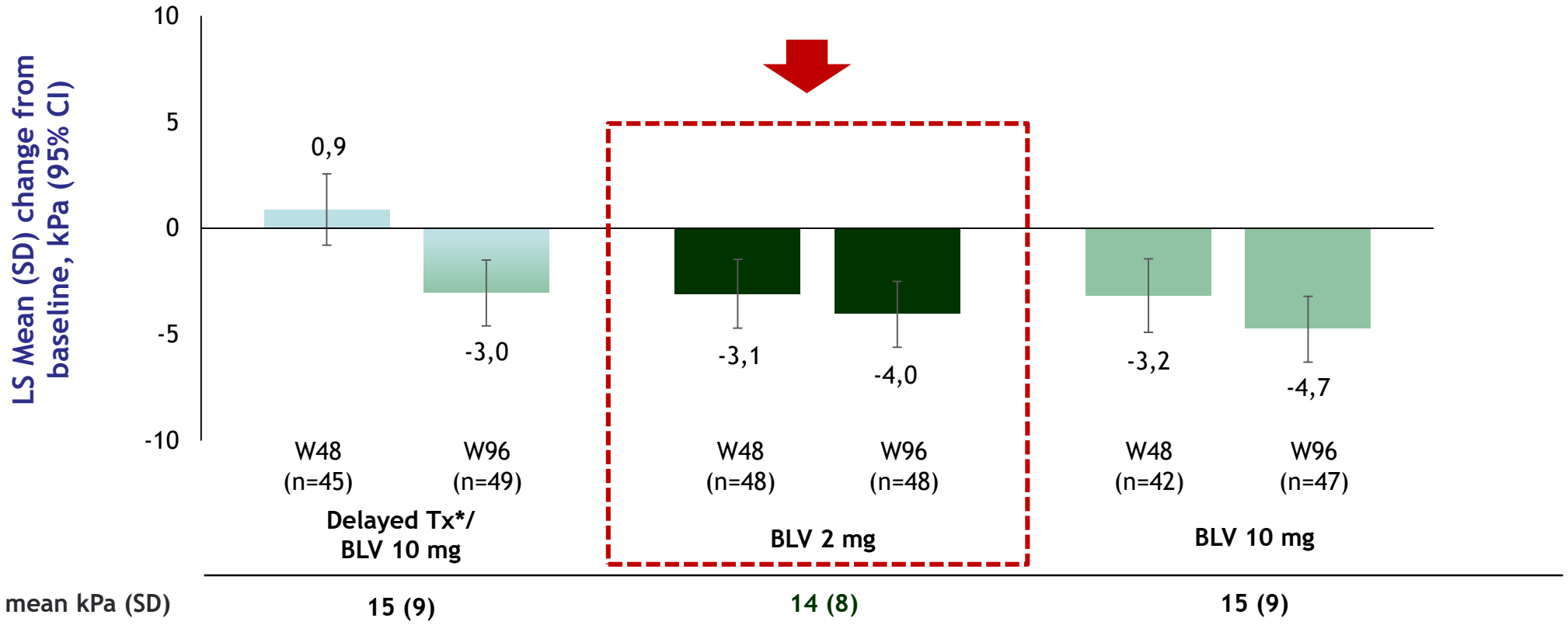
See poster #SAT-156

Suboptimal early virological response was defined as nonresponse or partial response at Week 24.
*Virological partial responders had an HDV RNA decline of ≥1 but <2 $\log_{10}$ IU/mL from baseline.
†Virological non-responders were defined as having an HDV RNA decline of <1 $\log_{10}$ IU/mL from baseline;
‡Patients received BLV 2 mg or 10 mg. BLV 2 mg is the only approved dose.
ALT: alanine aminotransferase; BL: baseline; BLV: bulevirtide.

Lampertico P, et al. EASL 2023. Poster #LBP-20.

Interim Efficacy Analysis at Week 96

Change in Liver Stiffness Measurement by Transient Elastography



BLV 2 mg and 10 mg were associated with continued reduction in liver stiffness through Week 96

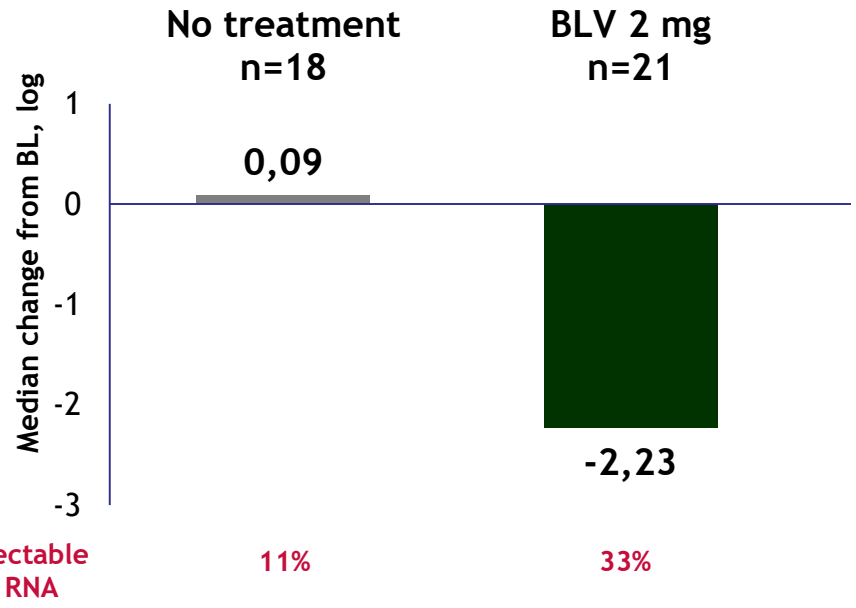
*Delayed treatment arm did not receive any BLV through Week 48. BLV, bulevirtide; LS, least-squares; LSM, liver stiffness measurement; Tx, treatment.

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

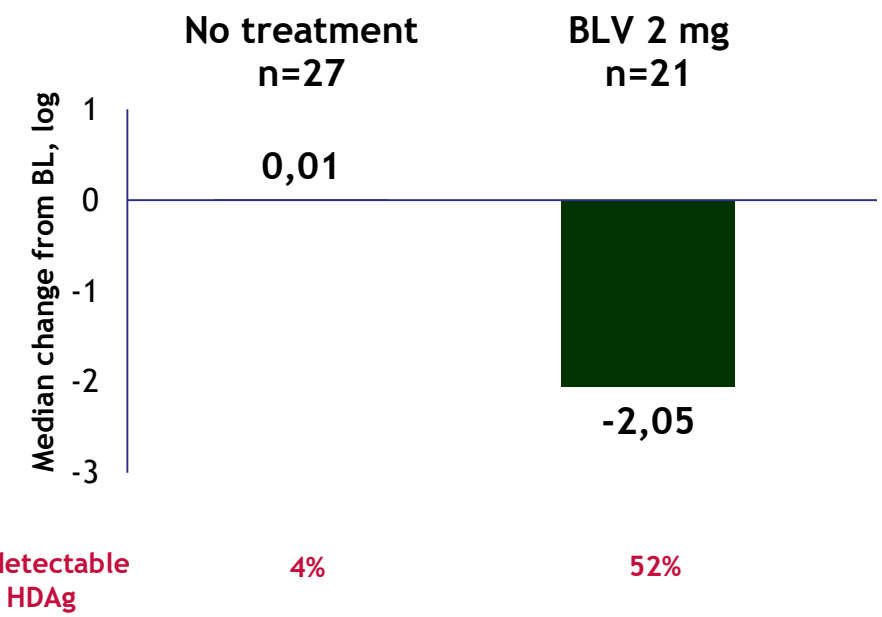
MYR 301 study
BLV 2 mg monotherapy for 48 weeks - Intrahepatic virological responses

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

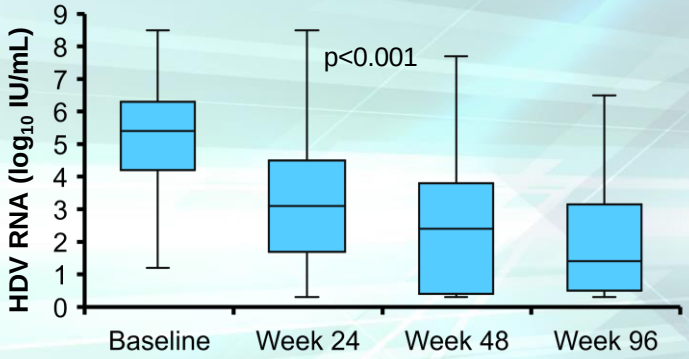
SAVE–D study
Effectiveness and safety of BLV 2 mg monotherapy up to 96 weeks in a real-world compensated cirrhotic cohort

SAVE-D: Retrospective, multicentre, pan-EU cohort of 176 patients from 37 centres*

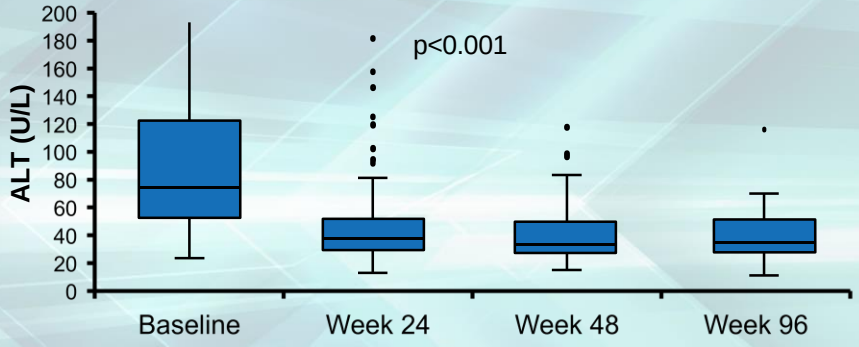
Baseline characteristics

Baseline characteristics	BLV 2 mg n=176
Median age, years (range)	50 (19–82)
Male, n (%)	104 (59)
HIV coinfection,† n (%)	15 (9)
CPT score A,‡ n (%)	176 (100)
Esophageal varices,§ n (%)	65 (54)
Previous ascites, n (%)	21 (12)
History of HCC,¶ n (%)	15 (9)
Median liver stiffness, kPa (range)	18.3 (6.4–75.0)
Median ALT, U/L, (range)	77 (23–1074)
Median platelets, median 10^3/mm^3 (range)	89 (17–330)
Median HDV RNA, $\log_{10}$ IU/mL (range)	5.4 (1.2–8.5)
NA treatment, n (%)	160 (91)
Previous IFN treatment, n (%)	103 (59)

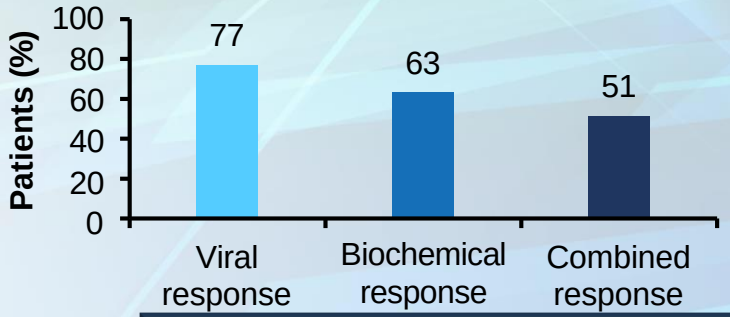
HDV RNA levels



ALT levels



Efficacy at Week 96



Safety profile:
BLV 2 mg led to elevations in bile acids. Mild pruritus was reported in 18 (10%) patients

*Cer

Improved albumin levels and low rates of decompensating events (but not of HCC)……

Degasperi E, et al. 23rd HDIN meeting; 21 June 2023.

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

(A) Subanalysis of patients with complete paired data (Baseline-week 48)
(B) Subanalysis of patients with complete paired data (Baseline-week 96)

*repeated analysis of variance (ANOVA); Values are expressed as number (percentage) or median (range)

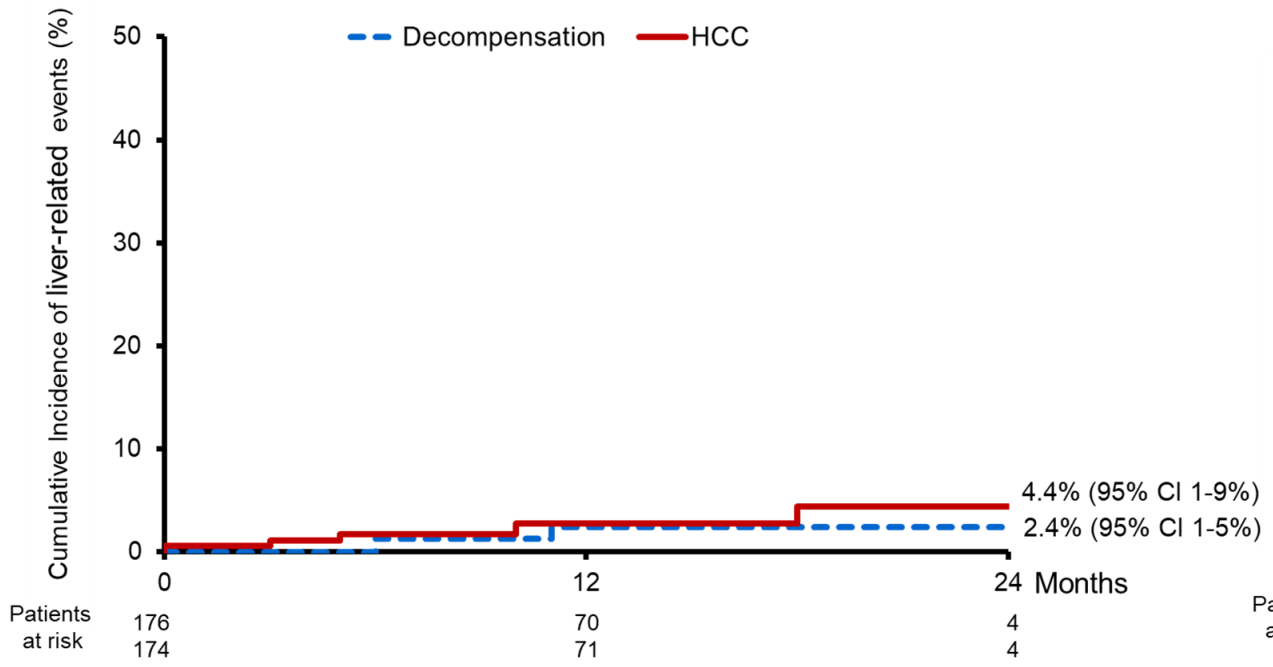
Degasperi E et al, Poster EASL 2023 LBP-11; Deltacure 2023 Poster #40, manuscript drafted

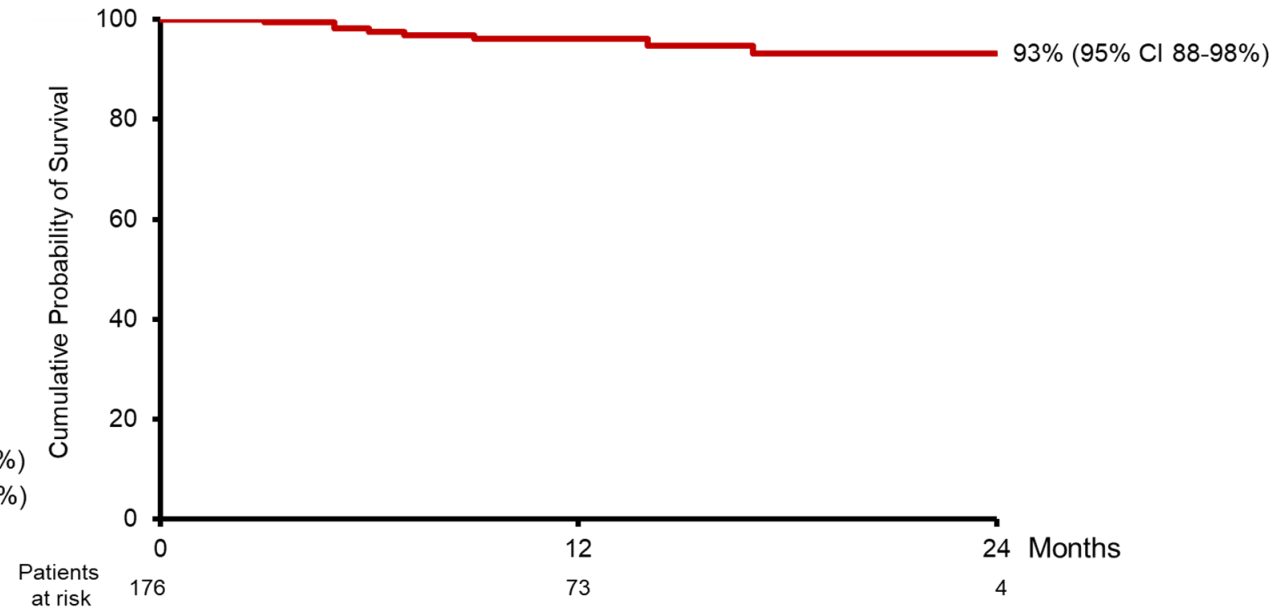
SAVE-D study
Clinical Outcomes during BLV Treatment

European, multicenter, retrospective real-world study (176 patients with cirrhosis enrolled)

8 liver-related events
- n=5 de-novo HCC
- n=3 decompensation (n=2 ascites, n=1 variceal bleeding)

8 deaths/LT
- 6 LT (n=4 for HCC, n=2 for ESLD)
- 2 deaths (pneumonia; intestinal infarction, BLV-unrelated)





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

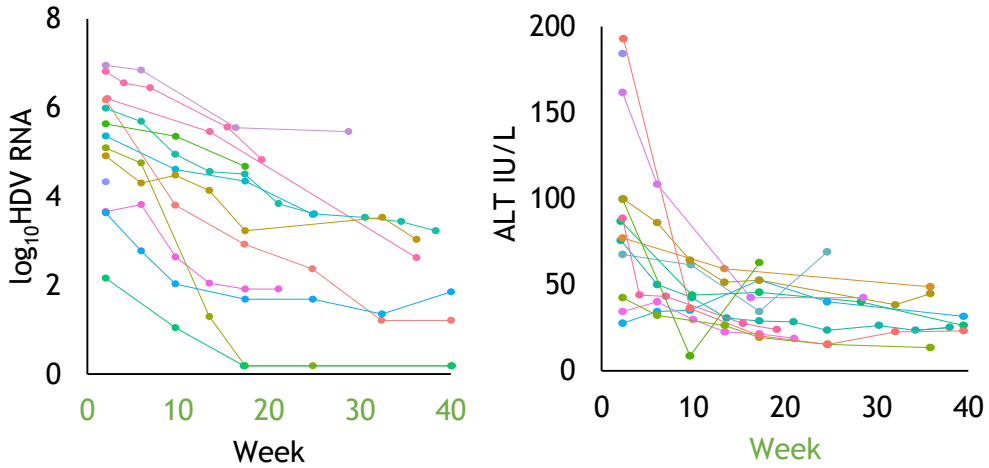
BLV monotherapy in patients with HDV-related decompensated cirrhosis (Child-B) – off-label use

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

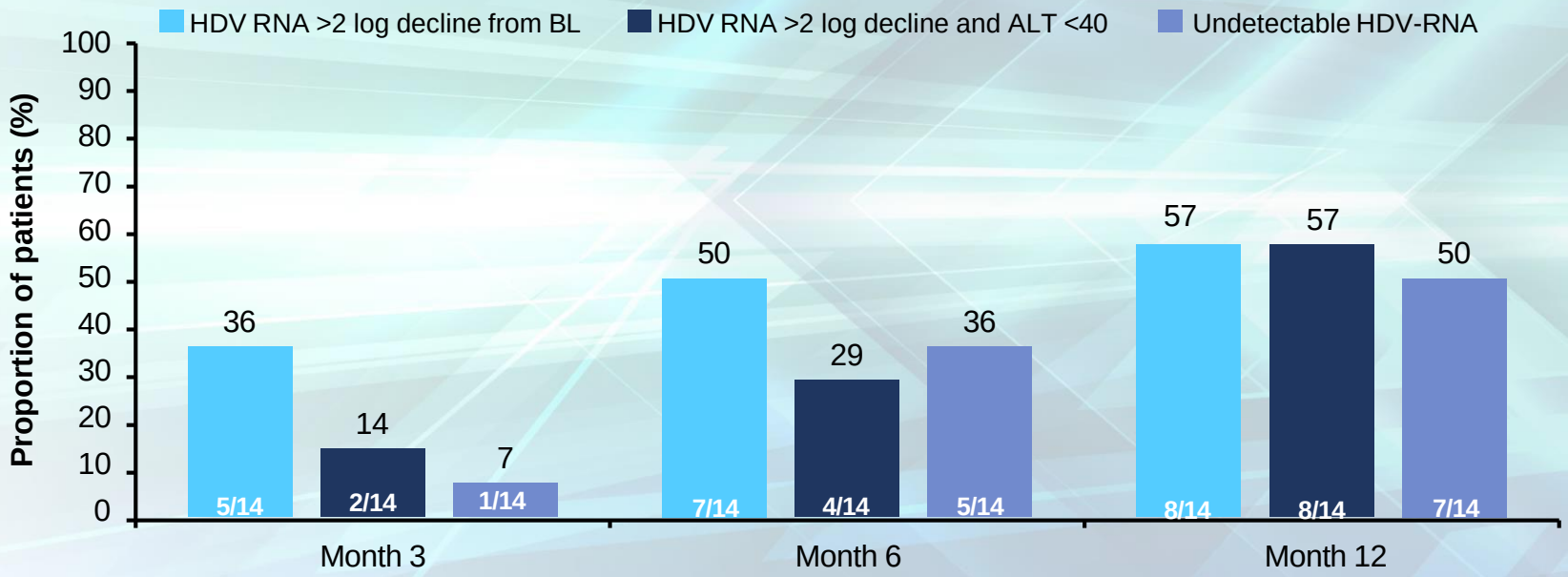
BLV 2 mg monotherapy is effective and well tolerated in people with HIV/HBV/HDV coinfection

cATU: First real-world cohort of HIV/HBV/HDV-coinfected patients treated with BLV 2 mg ± PEG-IFN

Baseline characteristics	Total n=21
Age, mean years	48
Male, %	71
HIV, %	100
Cirrhosis, %	52
HDV RNA, median log_{10} IU/mL	6.09
HIV RNA, median cp/mL*	0
CD4, median /mm3	558

Safety profile	Total n=21
AE related to BLV, n	0
HIV drug modifications, n	0
CD4, median / mm3 @ M12	540
Stopped treatment by M12, n (%)†	8 (38)

Virological and biochemical response: BLV 2 mg monotherapy (n=14, ITT analysis)

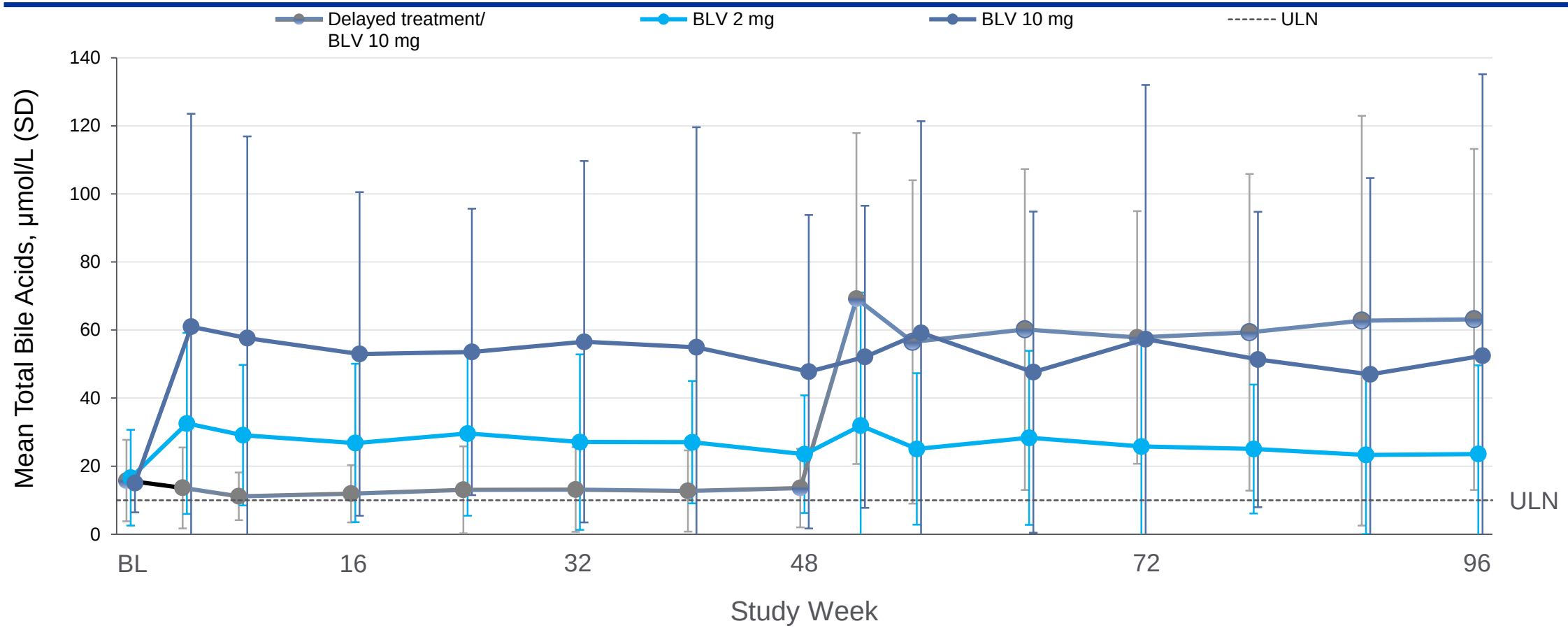


BLV 2 mg for up to 12 months was effective and well tolerated with no impact on CD4, HIV viral suppression or HIV treatment regimen

Visco Comandini U et al, HIV Med 2023: 14 HIV/HDV patients with comp cirrhosis and CSPH treated with BLV monotherapy……progressive increase of CD4/CD8 cells…no safety signals…

de Lédinghen V, et al. CROI 2023. Poster #589.

MYR301 study
Safety profile of 96 weeks BLV monotherapy for CHD

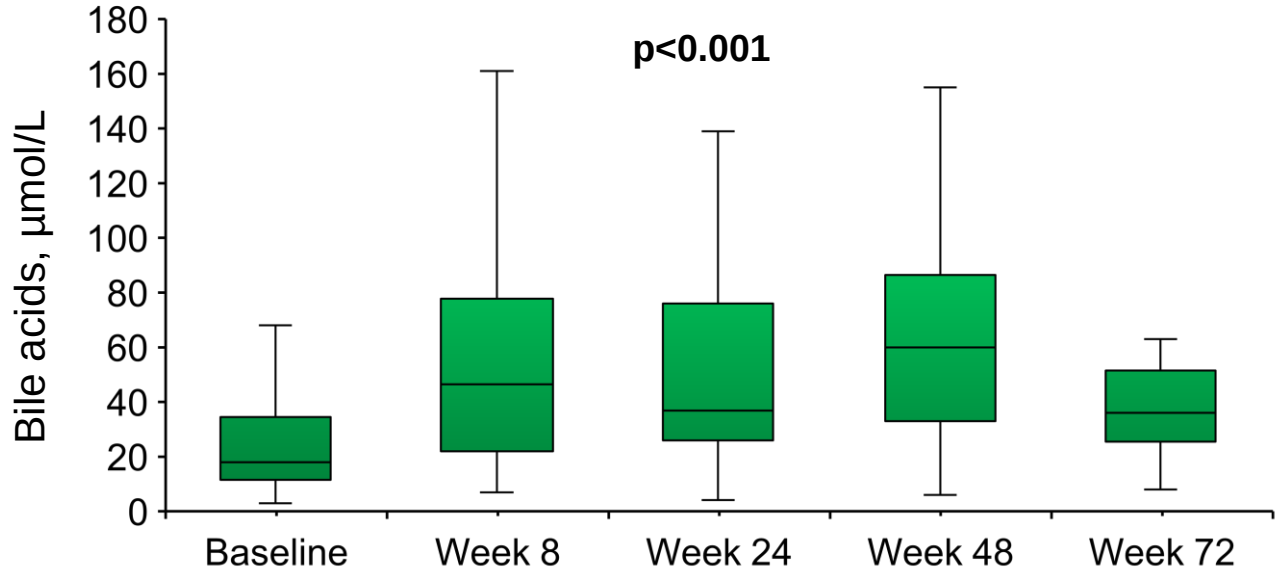


Dose-dependent asymptomatic elevations in total bile acids were observed with BLV treatment which were less pronounced in the 2 mg dose group

Safety analysis set. BLV, bulevirtide; ULN, upper limit of normal.

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

HEP4Di study
Extension of BLV 2 mg monotherapy up to 72 weeks in patients with compensated CHD-related cirrhosis



	Baseline	Week 8	Week 24	Week 48	Week 72
Median (range)	18 (3-306)	47 (7-490)	37 (4-748)	63 (6-416)	36 (8-173)

BLV-related AEs

- Significant bile acids elevation
- Mild, transient pruritus in n=12 (13%)
- Injection site reactions in n=6 (6%)
- No discontinuations due to BLV-related AEs

Liver-related events and death/OLT

- N=2 decompensating events (n=1 ascites with portal vein thrombosis; n=1 variceal bleeding)
- N=5 with de-novo HCC
- N=5 undergoing liver transplantation (n=3 for HCC, n=2 for ESLD)
- N=1 death due to pneumonia (BLV-unrelated)

Degasperi E et al, AISF 2023

Bulevirtide (BLV) for CHD: current challenges

- Patient adherence is relevant (daily sc injections)
- Long-term suppressive therapy (optimal duration currently unknown)
- Monotherapy vs combination with pegIFN ? (combo for few patients ?)
- No HBsAg decline/loss, rare HDV cure
- 10-20% primary virological non response (but normal ALT levels ?)
- 20% undetectable HDV RNA at year 1 (but increasing over time ?)
- Safety data beyond week 48-96 very limited (and increase of BA)
- Clinical efficacy: no data on hard clinical endpoints (but albumin levels increase)
- …….

Bulevirtide added to recommendations in 2022–2023

EACS 2022
ICONA 2023

Bulevirtide use in patients with HIV/HBV/HDV co-infection[1,2]

DGVS 2023

Guidance on bulevirtide for hepatitis delta[3]

- **All patients** with chronic HDV infection and detectable HDV RNA **should be evaluated** for therapy
- Patients with high inflammatory activity, **advanced fibrosis and/or compensated liver cirrhosis should be treated as a priority**

EASL 2023

First international guidelines for hepatitis delta

EASL CPG presentation: HDV | Saturday 10.45 CEST, Room Lehar 3

CHMP 2023

Bulevirtide recommended for full marketing authorisation[4]

1. EACS Guidelines 2022 v11.1. Available at: https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf; 2. ICONA Foundation. Available at: www.fondazioneicona.org/_new2/download/ICONA_DocumentoDiIndirizzo2023.pdf; 3. Sandmann L, et al. Antiviral therapy of chronic hepatitis D virus 2023. Available at: https://www.dgvs.de/wissen/leitlinien/leitlinien-dgvs/hepatitis-b (All accessed June 2023); 4. Gilead Sciences. Press Releases. Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2023/5/chmp-adopts-positive-opinion-recommending-hepcludex-bulevirtide-for-full-marketing-authorization-for-the-treatment-of-hepatitis-delta-virus-hdv.

CHMP: Committee for Medicinal Products for Human Use;
CPG: Clinical Practice Guidelines;
DGVS: German Society for Gastroenterology, Digestive and Metabolic Diseases;
EACS: European AIDS Clinical Society;
EASL: European Association for the Study of the Liver.

Bulevirtide in Italy for CHD since 2023

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 164° - Numero 20

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La **Gazzetta Ufficiale, Parte Seconda,** *"Foglio delle inserzioni", è pubblicata il martedì, il giovedì e il sabato*

- Art. 1. *Classificazione ai fini della rimborsabilità* ……. è indicato per il trattamento dell'infezione cronica da virus dell'epatite delta (HDV) in **pazienti adulti positivi a HDV-RNA plasmatico (o sierico) con malattia epatica compensata.**
- ……..
- Art. 3. *Classificazione ai fini della fornitura*
  La classificazione ai fini della fornitura del medicinale «…….» (bulevirtide) è la seguente: medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di **centri ospedalieri o di specialisti - internista, infettivologo, gastroenterologo** (RNRL).

Hepcludex 2 mg/day sc ordinabile/disponibile dal 1 Maggio 2023

Determina del 13 Gennaio 2023, pubblicata il 25 Gennaio 2023

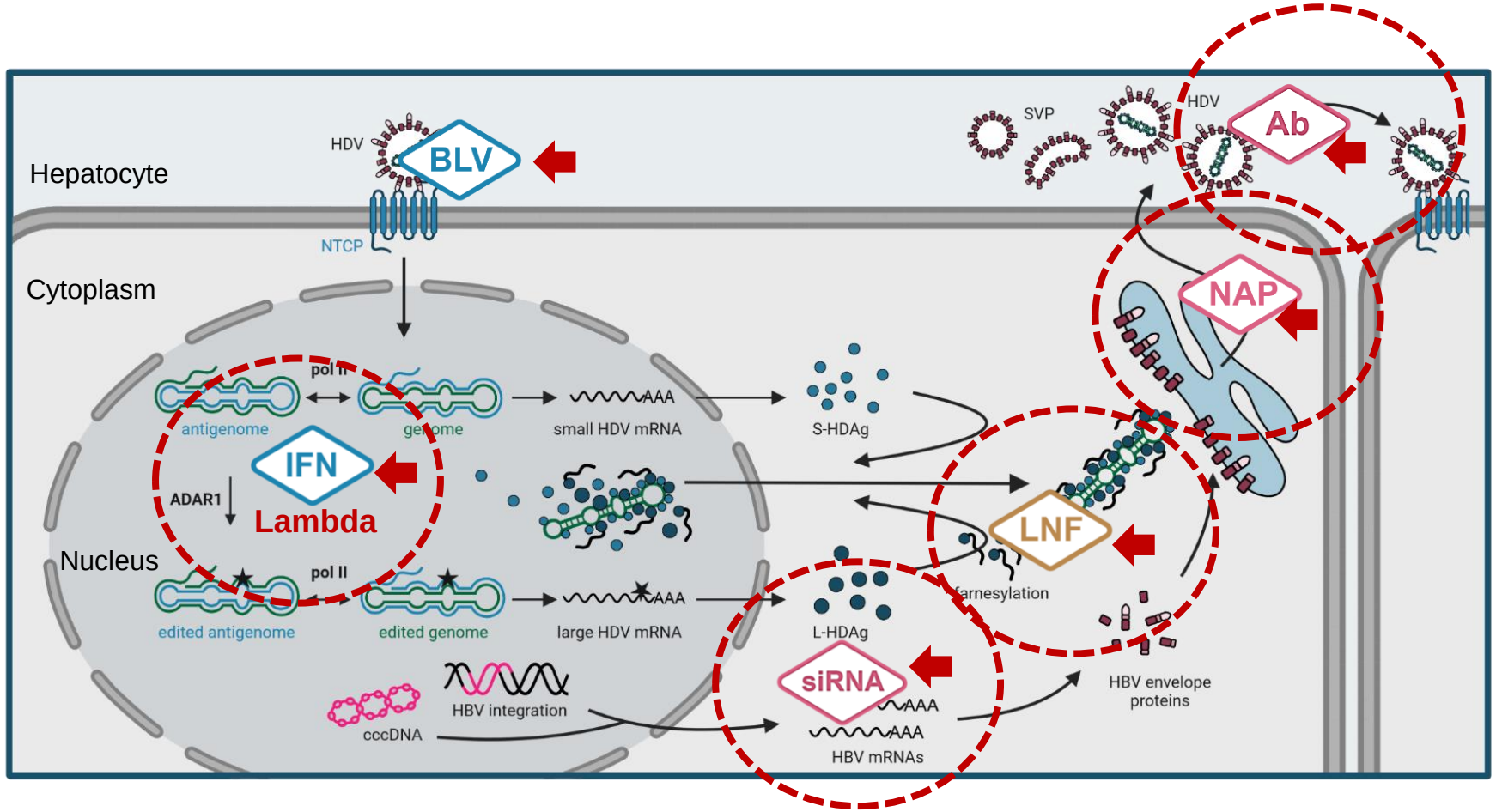
D-SHIELD study
Effectiveness and safety of Bulevirtide (BLV) treatment in CHD in Italy

Study Design	Prospective, multicenter, nationwide, investigator-driven, real-world
Enrolling Centers	Hepato/Gastro/ID/IM units in Italy
Inclusion Criteria	CHD patients starting BLV (± pegIFNα) from May 1st, 2023
Treatment	BLV 2 mg/day self-administered (subcutaneous injection*)
Monitoring	Baseline and every 8/12 weeks
Endpoints	Virological, biochemical and clinical responses
Ethical Committe	14 Mach 2023 (Milan)
Contacts*	E Degasperi, MP Anolli (IRCCS Fondazione Policlinico, Milan)
Database	Excel® → REDCap®
Support	Data entry, data analysis, publication

*Email: elisabetta.degasperi@policlinico.mi.it; maria.anolli@unimi.it

September 2023

Therapeutic targets for HDV infection



NUC therapy for HBV does not directly interfere with HDV replication

Courtesy of L. Allweiss/A. Volmari, adapted from Dandri et al J. Hepatol 2022

New anti-HDV therapeutics - Summary

- From 1977 to 2020, no EMA or FDA approved therapy for HDV has been available
- In 2020, EMA approved BLV 2 mg for compensated CHD (available in EU)
- BLV monotherapy is safe and effective up to 96 weeks even in compensated cirrhotics with CSPH and in Child-B patients (few data).
- BLV as long-term BLV monotherapy for most patients.
- Stopping rules for BLV: long-term HDVRNA undetectabilty (>1-2 years)?
- Other therapeutic approaches under development…….

Overall, many new encouraging data but an easy to use, short-term, curative oral therapy to cure HDV patients is not yet available

Thank You for Your Attention!

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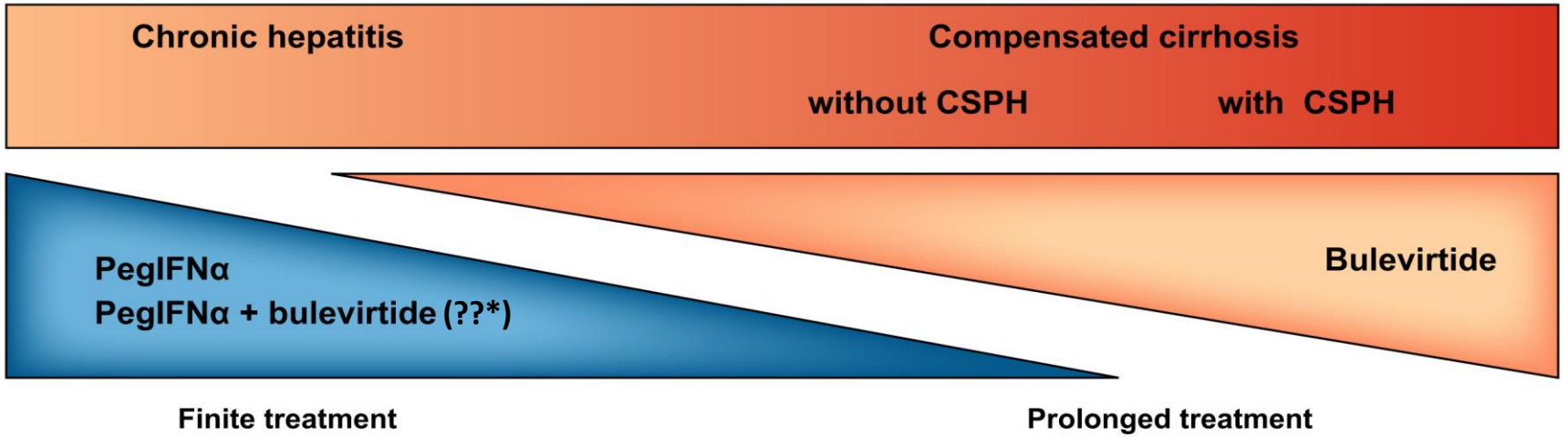
DEGLI STUDI
DI MILANO

Back-up slides

Management of antiviral treatment in patients with CHD



Additional factors influencing the 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

No anti-HDV therapy approved for decompensated cirrhosis (liver transplantation)

***De-novo combination pegIFNα + BLV: no studies published so far**

modified from EASL 2023 HDV guidelines, J Hepatol 2023