



17 May 2024

## Hepatitis Delta treatment: 2024 update

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## 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 ~300 million HBsAg carriers, 10-20 million are also anti-HDV positive (rare disease)
- Diagnostics: screening by anti-HDV (reflex test ?), diagnosis by HDV RNA (assay?)
- 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

## Bulevirtide (BLV) is an HDV entry inhibitor (2 mg/day sc injection) (EMA approved in 2020-2023)



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

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#### BLV is a specific inhibitor of the NTCP bile acid transporter, the entry receptor for HDV<sup>2</sup>

 Zhang Z, Urban S. J Hepatol 2021;74:686-99; 2. Kang C, Syed YY. Drugs 2020;80:1601-5;
 EMC. HEPCLUDEX ▼ (bulevirtide) Additional monitoring SmPC. Available at: https://www.medicines.org.uk/emc/product/13482 (accessed July 2023).

**BLV** does not <u>directly</u> inhibit HDV replication in infected cells!

## Efficacy of BLV monotherapy

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





CONS: no HBsAg decline, no HBsAg loss and only 10-20% undetetectable HDV RNA

\*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 #0S093; 5. Killer A, et al. EASL 2022. Poster #SAT345

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





## MYR203 and 301 studies Intrahepatic responses after 48 weeks of BLV monotherapy





#### Intrahepatic HBsAg levels



• Serum and liver HDV RNA levels strongly correlated (Spearman r: 0,62, p <-0.0001)

• Liver HDV RNA negative (<LLOQ): 37% and 62% in 2 and 10 mg arms, respectively

• Liver HDAg negative staining: 50% and 54% in 2 and 10 mg arms, respectively

Blocking viral entry diminishes signs of liver inflammation and promotes a strong reduction of HDV infection within the liver, thus suggesting that some patients may achieve HDV cure with long-term treatment

## SAVE-D study Virological and biochemical responses during BLV monotherapy



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

**BLV** monotherapy is effective also in compensated cirrhotics ± CSPH

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 <sup>3</sup> /mm <sup>3</sup>	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
lgG, 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)

**BLV 2 mg monotherapy significantly improves liver tests and NITs** 

Anolli MP et al, AISF meeting March 2024

## SAVE-D study Liver-related events during long-term BLV monotherapy

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



# 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)	Efficacy Responses						
Child-Pugh Stage, n		Dots and lines represent individual patients (n=13)						
А	<b>1</b> †	8 200 virologic response**						
В	14	$\leq 6$ 150 7 of 15 patients had						
Ascites, n	10	$\frac{1}{2}$ ALT normalization						
Variceal bleeding history, n	2	H G A of 15 patients improved						
Esophageal varices present, n	13	<sup>3</sup> 2 50 from Child-Pugh B to A						
Bilirubin, µmol/L (mean ± SD)	36.1 ± 24.6	0 0 10 20 30 40 0 0 10 20 30 40 27% 4 of 15 patients had improvement of ascites						
(>34.2 µmol/L), n	6	Week Week						
Albumin, g/dL (mean ± SD) Hypoalbuminemia (<35 g/dL), n	33.0 ± 4.6 9	<ul> <li>Safety profile:</li> <li>1 patient experienced worsening of liver function after add-on pegylated IFN (not related to BLV)</li> <li>1 patient experienced further decomposition after TIPS insertion and incarceration of hernia (not related to BLV)</li> <li>3 patients terminated BLV therapy at liver transplantation</li> </ul>						

#### 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  $\geq 2 \log$ ; <sup>†</sup>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. Hepatology 2024

## 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



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: 5 HIV/HDV patients with comp cirrhosis and CSPH treated with BLV monotherapy.....progressive increase of CD4/CD8 cells...no safety signals...

## 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

## Can we <u>cure</u> HDV with BLV monotherapy ?

## A 3-year course of BLV monotherapy <u>may cure HDV without HBsAg loss</u> The "Milan patient"

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



#### Virological and biochemical response during and off BLV therapy

# H&E staining Masson staining HBsAg staining HDAg staining

#### 2nd liver biopsy performed at week 48 off-therapy

- 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.</p>
- > 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)

#### 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 <u>without</u> HBsAg loss

#### **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

#### Can we stop BLV monotherapy after 2 years 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 RNA Undetectability 24 weeks after BLV STOP



Mi II r

#### 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

## MYR301 study Phase 3 Trial of Bulevirtide Monotherapy in Patients with CHD

Multicenter, open-label, randomized, Phase 3 study, conducted in 4 countries (Germany, Italy, Russia, Sweden)



#### Primary Study Endpoint (Week 48):

Proportion of patients achieving the **Combined response** 

HDV RNA undetectable or decrease of ≥2 Log<sub>10</sub> IU/mL from baseline and ALT normalization

#### BLV 10 mg, dosing not authorised for clinical use

#### **Off-therapy results in 2025 ?**

#### Week 96 Analysis Endpoints:

Proportion of patients with:

- HDV RNA decrease of ≥2 Log<sub>10</sub> IU/mL from baseline or undetectable HDV RNA
- Undetectable HDV RNA
- ALT normalization
- Change in liver stiffness
- Adverse Events

Materiale reso disponibile da Gilead Sciences Srl, relativo ai lavori del Convegno "PIONERS In viral research Hepatitis & Covid-19" del 31 ottobre 2023 - Milano Il materiale è esclusivamente riservato agli operatori sanitari partecipanti al convegno. Non è consentito l'utilizzo per finalità diverse dalla consultazione dei testi. La riproduzione, la copia e divulgazione sono rigorosamente vietate. LIV 23047

## **Efficacy of BLV + pegIFNα combination?**



## **MYR204 Study Design**



<sup>16</sup> \*Undetectable HDV RNA defined as <LLOQ, target not detected. LLOQ <50 IU/mL; limit of detection: 6 IU/mL; \*\*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). ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; IFN, interferon; LLOQ, lower limit of quantification; PegIFNα, pegylated interferon alpha; ULN, upper limit of normal. Asselah T, et al. AASLD 2023. Oral #5009</p>



## Efficacy Analysis 24 Weeks After EOT



#### BLV + PegIFNα resulted in higher rates of undetectable HDV RNA and ALT normalization

\*Only significant comparison by Fisher's Exact Test, p value <0.05 are shown on graph; Full Analysis Set, Missing=Failure; \*\*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). ALT, alanine aminotransferase; BLV, bulevirtide; EOT, end of treatment; LLOQ, lower limit of quantification; PegIFNα, pegylated interferon alpha.</p>
Asselah T, et al. AASLD 2023. Oral #5009

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## **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

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

- Treatment with JNJ-3989 led to robust reductions in HBsAg and HDV RNA
- 12/17 patients in the immediate active treatment arm experienced ALT elevations\* with 8 leading to treatment discontinuation prior to Week 48

**Primary endpoint:** HDV RNA ≥2 log<sub>10</sub> IU/mL decline from baseline or HDV RNA TND with normal ALT at Week 48

ious Diseases



• 4/5 (80%) patients in active treatment arm without ALT elevation\* achieved primary endpoint (2 patients HDV RNA < LLOQ)

SE, standard error. \*confirmed ALT ≥3x ULN and ≥2x nadir

#### H. Wedemeyer et al. EASL 2023 OS-030

## REEF-D study (part 1) Baseline Factors Associated With ALT Elevations\*



• ALT elevations\* were more frequent in patients with high screening HBsAg and HDV RNA levels

21 patients receiving JNJ-3989 were included in this analysis (1 deferred active treatment arm patient with cirrhosi \*Confirmed (2 consecutive visits) ALT  $\ge$ 3 × ULN and  $\ge$ 2 × nadir.

#### H. Wedemeyer et al. EASL 2023 OS-030

#### Update of the REEF-D study at EASL 2024

## **Therapeutic targets for HDV infection**



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

## SOLSTICE study VIR 2218 (siRNA) and VIR 3434 (moAb) for CHD - Week 12 preliminary data

	VIR-2218 Q4W (Cohort 1A) N = 5	VIR-3434 Q4W (Cohort 1B) N = 6	VIR-2218+3434 Q4W (Cohort 2C) N = 6 <sup>a</sup>
HDV Virologic Response <sup>b</sup> , n (%)	1 (20)	3 (50)	5 (100)
Reduction from Baseline in HDV RNA (log <sub>10</sub> IU/mL), Median (IQR)	-1.39 (-1.51, -1.04)	-1.98 (-2.82, -0.94)	-4.29 (-5.47, -3.93)
HDV RNA < LLOQ <sup>c</sup> , n (%)	1 (20)	2 (33)	5 (100)
HDV RNA < LOD <sup>d</sup> , n (%)	1 (20)	1 (17)	4 (80)
Reduction from Baseline in HBsAg (log <sub>10</sub> IU/mL), Median (IQR)	-1.35 (-1.52, -1.27)	-0.18 (-0.35, -0.09)	-3.88 (-4.03, -3.88)
ALT normalization <sup>e</sup> , n (%)	2 (40)	2 (33)	1 (20)
ALT (U/L), Mean (SD)	118.8 (145.5)	44.0 (19.5)	42.6 (7.5)
Combined Endpoint <sup>f</sup> , n (%)	0	1 (17%)	1 (20)

<sup>a</sup> Cohort 2C has 6 total participants enrolled with 5 participants reaching at least 12 weeks.

<sup>b</sup> Undetectable or  $\geq 2 \log_{10}$  decrease in HDV RNA.

° LLOQ <63 IU/mL, supplied by Robogene® 2.0 Assay was used to assess HDV RNA, supplied and analyzed by Viroclinics-DDL™.

<sup>d</sup> LOD <14 IU/mL, supplied by Robogene® 2.0 Assay was used to assess HDV RNA, supplied and analyzed by Viroclinics-DDL<sup>™</sup>.

 $^{\circ}$  ALT ≤ ULN: Female = 33 U/L; Male ULN = 40 U/L.

ALT, devia

<sup>f</sup>Combined Endpoint = undetectable  $or \ge 2 \log_{10}$  decrease in HDV RNA + ALT normalization.

Add-on rescue therapy in suboptimal responders at week 12 (from week 12 to 24)

Update of the SOLSTICE study at EASL 2024

r limit of quantification; LOD, limit of detection; Q4W, once every 4 weeks; RNA, ribonucleic acid; SD, standard

## **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).
- Long-term BLV monotherapy for most patients...but HDV cure for some....
- Other antiviral strategies under development (LNF±pegIFN, siRNA, moAb, REP....)
- New data at EASL 2024

#### In conclusion, BLV 2 mg monotherapy is the SOC treatment for CHD in 2024





## **Thank You for Your Attention!**