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# Antiviral treatment for HDV: lessons learned from Bulevirtide

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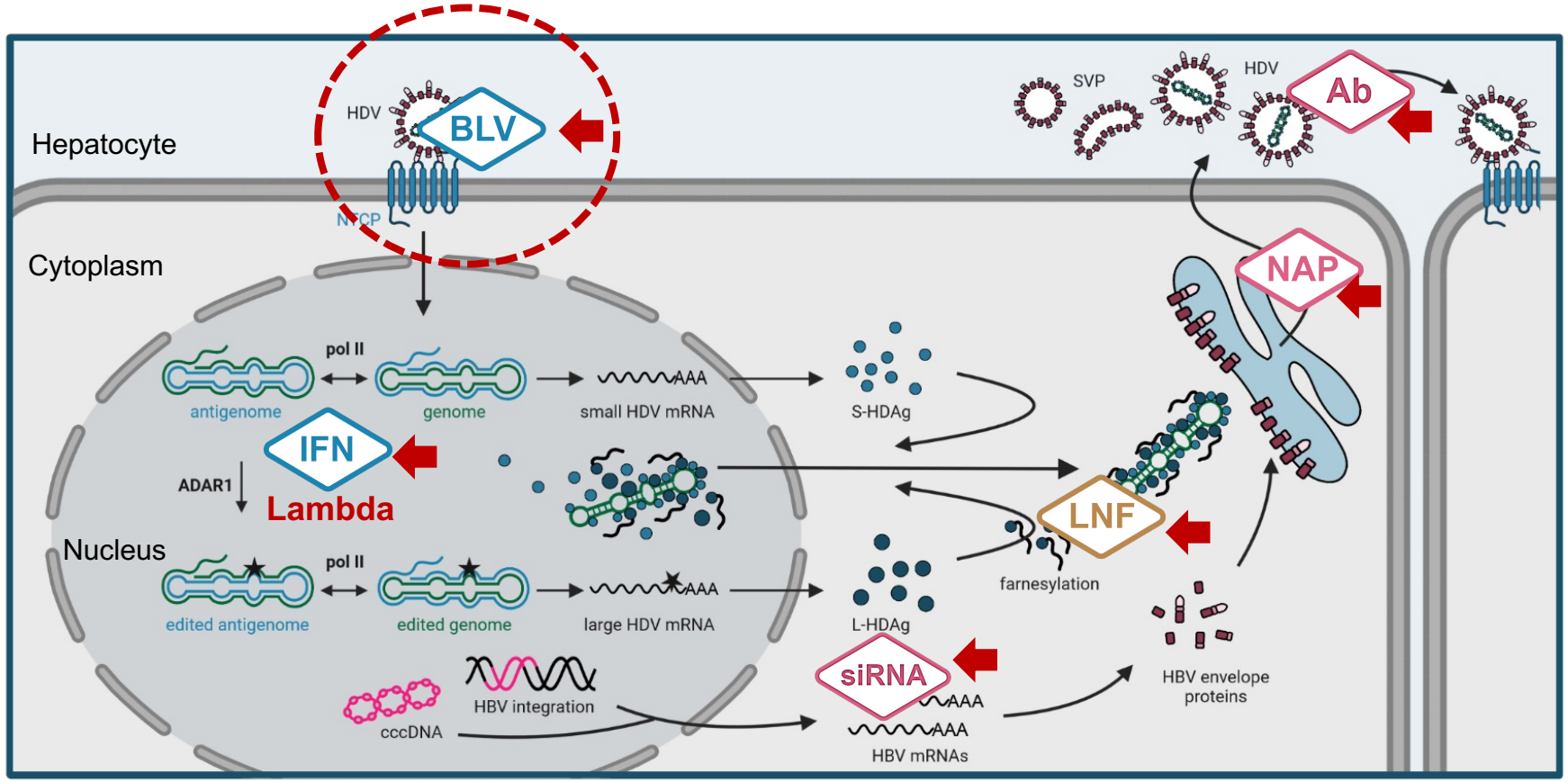
# Conflicts of interests

Advisory Board/Speaker Bureau for:

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

# Therapeutic targets for HDV infection

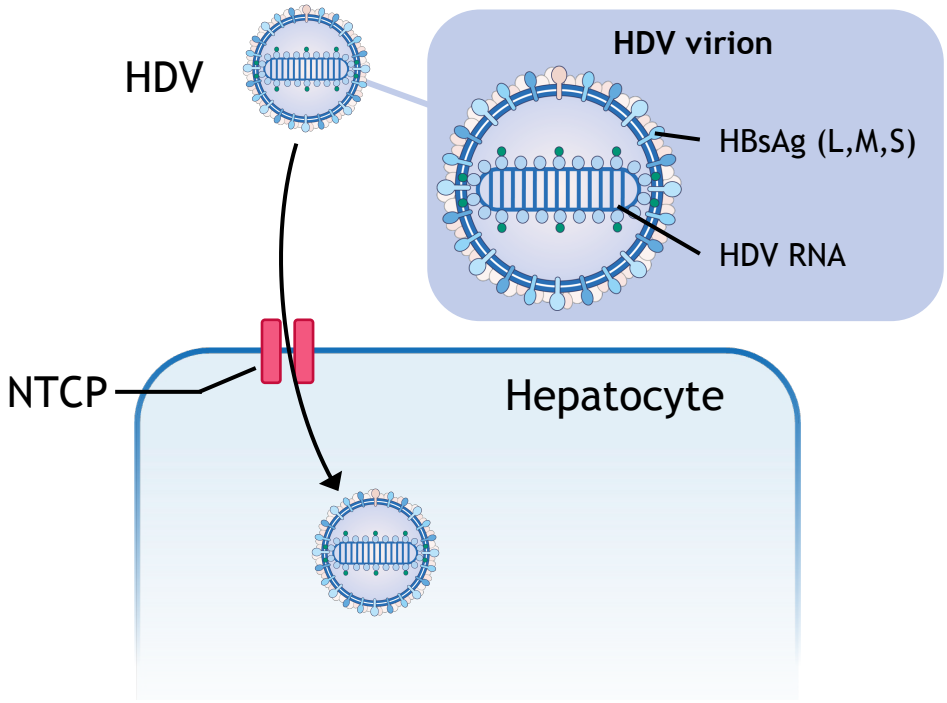



**NUC therapy for HBV does not directly interfere with HDV replication**

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

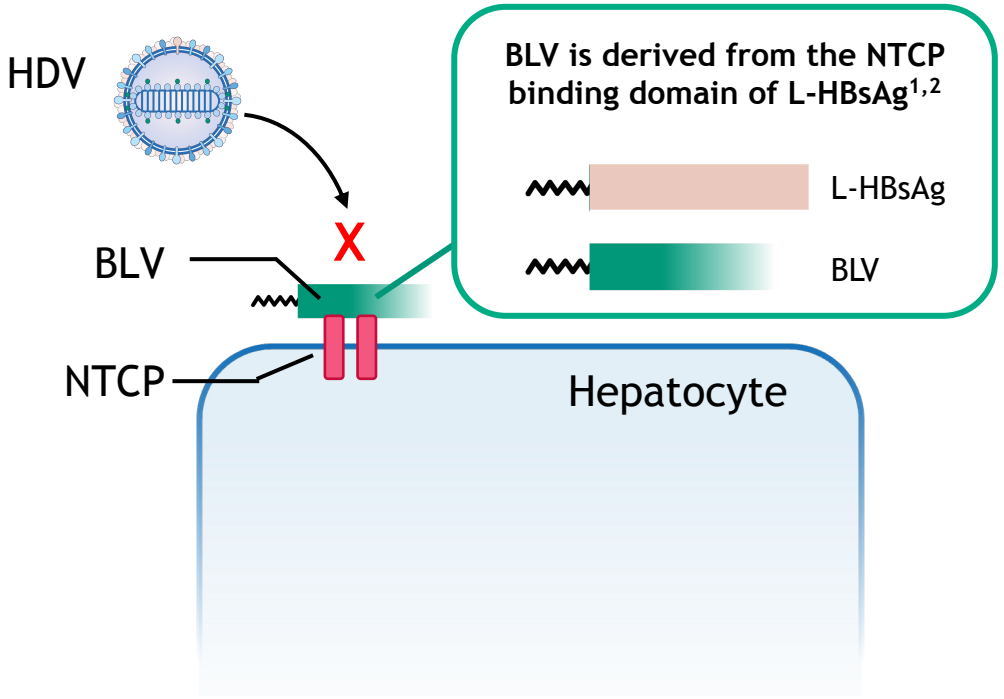
# Bulevirtide (BLV) is an HDV entry inhibitor (2 mg/day sc injection)
# Full EMA approval in 2023

## 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

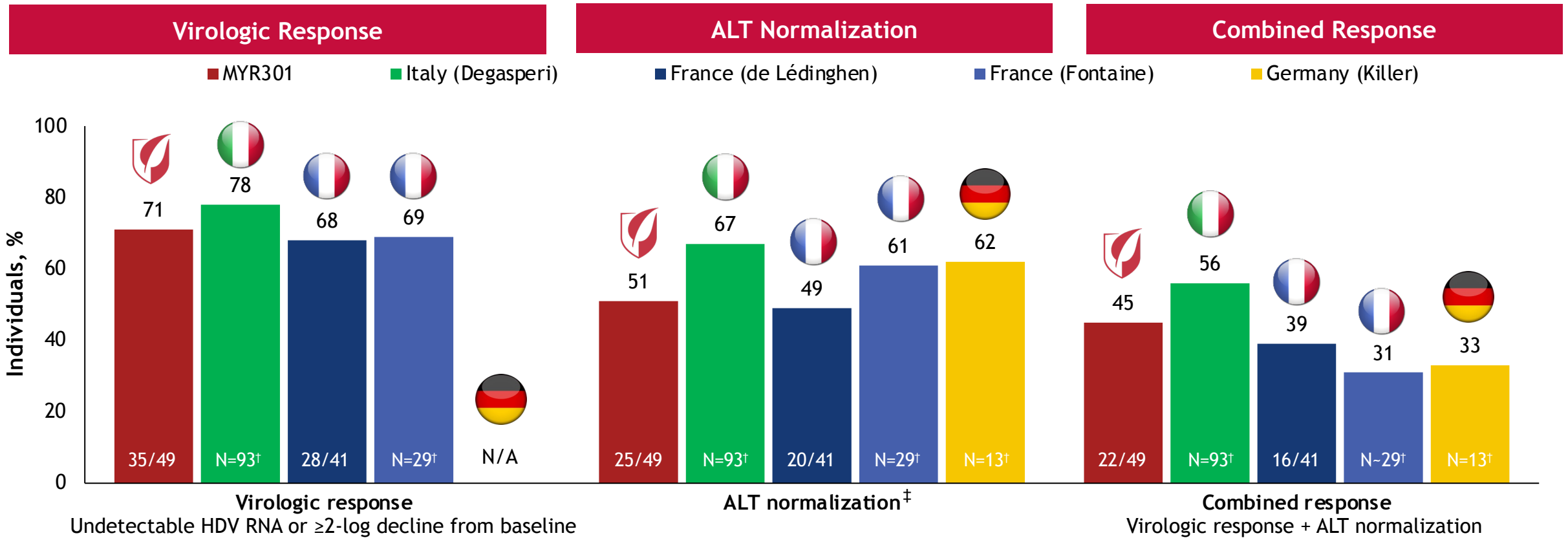
**BLV is a specific inhibitor of the NTCP bile acid transporter, the entry receptor for HDV[2]**

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 <u>directly</u> inhibit HDV replication in infected cells!**

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

*NOT HEAD-TO-HEAD COMPARISONS




**Why 10-20% of patients are virological non-responders ?**
**Why only 15-30% of the patients achieve undetectable HDV RNA ?**

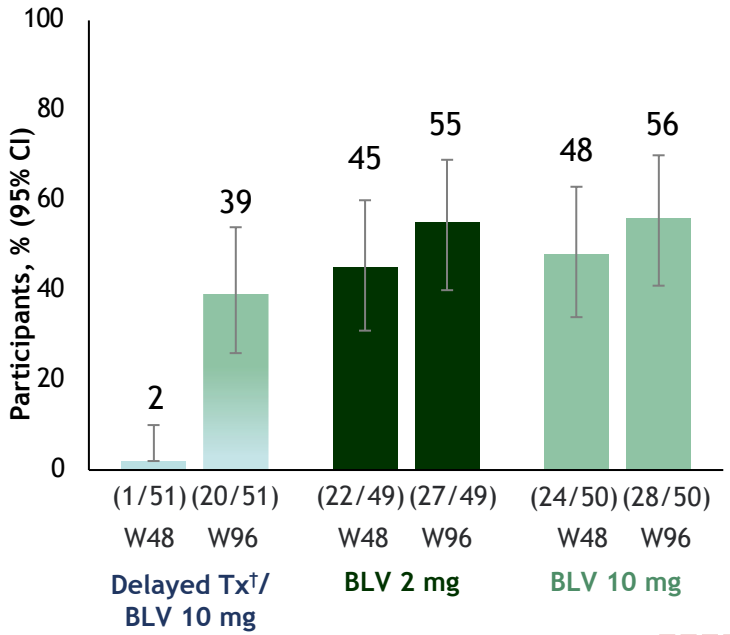
*NOT HEAD-TO-HEAD COMPARISONS. This graphic serves to illustrate outcomes obtained from different studies, which are therefore not directly comparable as study populations are NOT matched


*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 #OS093; 5. Killer A, et al. EASL 2022. Poster #SAT345*

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

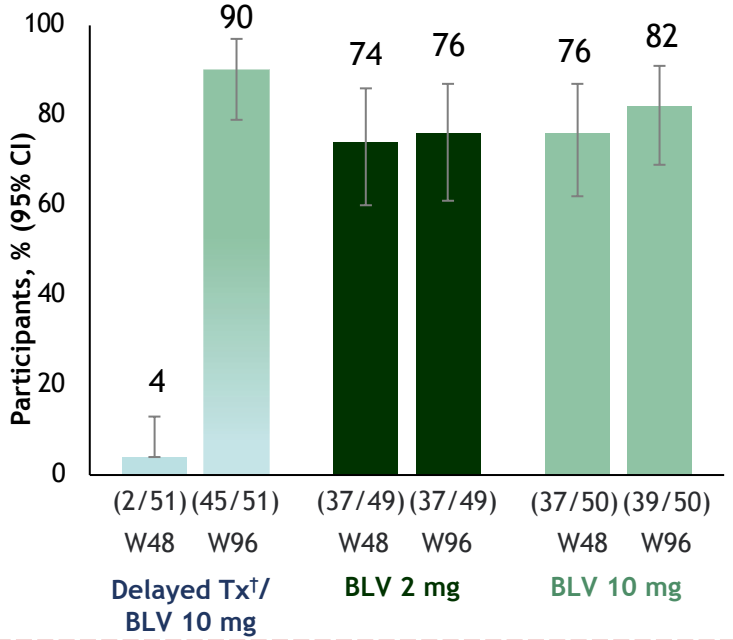
## Combined Response

**Undetectable HDV RNA* or ≥2 log10 IU/mL decrease from BL and ALT normalization**



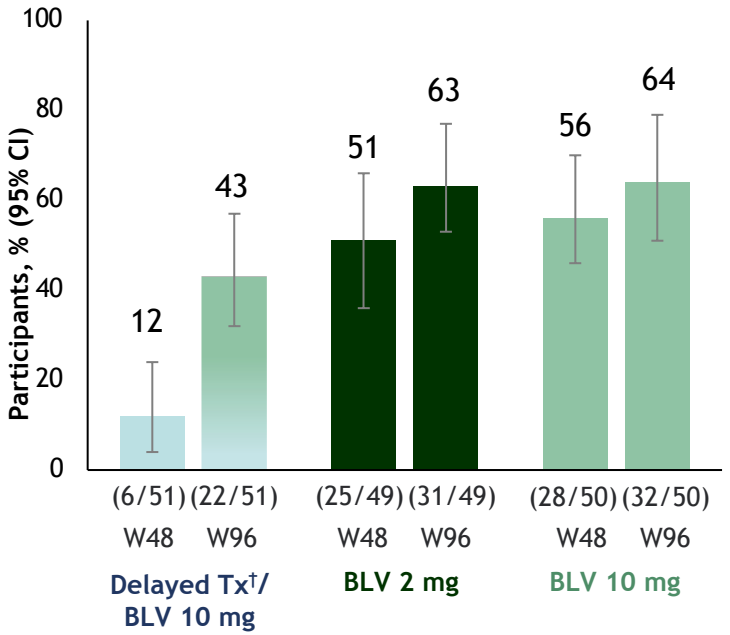

## Viral Response

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




## Biochemical Response

**ALT normalization ****




| Undetectable, % | 0 | 24 | 12 | 20 | 20 | 36 |
|---|---|---|---|---|---|---|

**Combined and Biochemical response increase with longer term BLV monotherapy**

**Is 2 mg/day the optimal dose of BLV monotherapy ?**

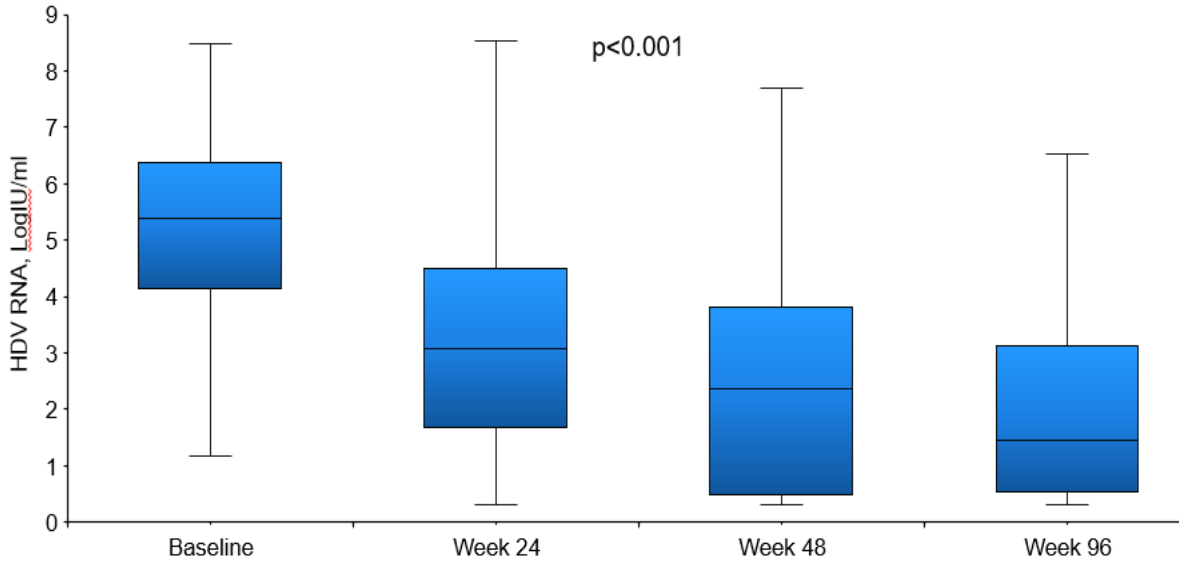
*Undetectable HDV RNA defined as below lower limit of quantification (target not detected) for women and ≤49 U/L for men; †Delayed treatment arm did not receive any BLV through W

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

# SAVE-D study
# BLV 2 mg monotherapy in HDV-related compensated cirrhosis

Retrospective, multicenter, real-world study (176 patients, 37 EU centers)

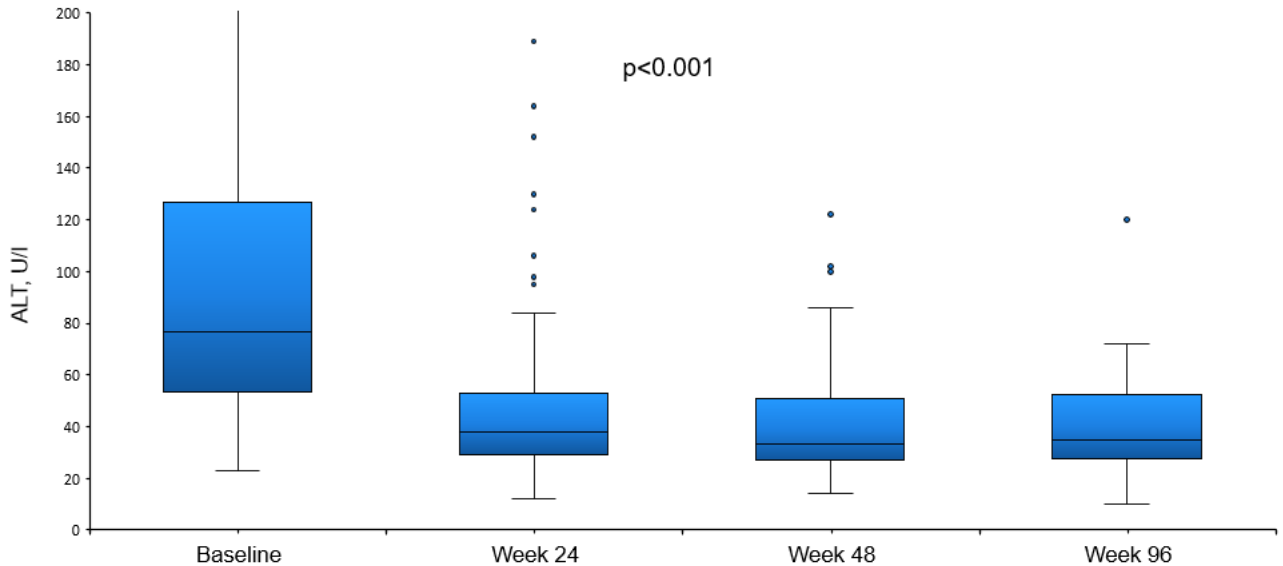
## HDV RNA levels




| | Baseline | Week 24 | Week 48 | Week 96 |
|---|---|---|---|---|
| Median<br>Range | 5.4<br>(1.2-8.5) | 3.1<br>(0.3-8.5) | 2.4<br>(0.3-7.7) | 1.5<br>(0.3-6.5) |
| **HDV RNA Decline (Log)** | | **1.9 (0.1-6.2)** | **2.8 (0.1-7.6)** | **3.2 (0.3-6.4)** |

**Why do we see this wide range of virological decline ?**

## ALT levels




| | Baseline | Week 24 | Week 48 | Week 96 |
|---|---|---|---|---|
| Median<br>Range | 77<br>(23-1,074) | 38<br>(12-189) | 34<br>(14-122) | 35<br>(10-271) |

**Why ALT response is faster than virological response ?**

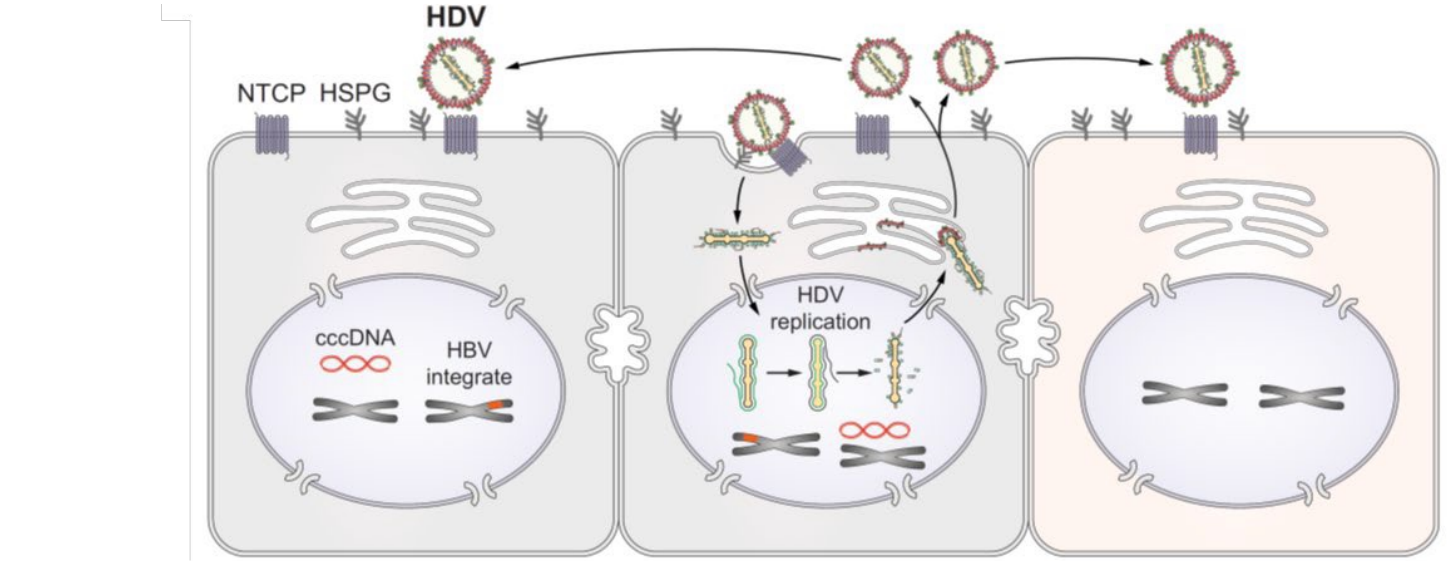
*Degasperi E. et al, EASL 2023 LBP-11*

# Variables likely to be involved in HDV clearance/inhibition in BLV-treated patients

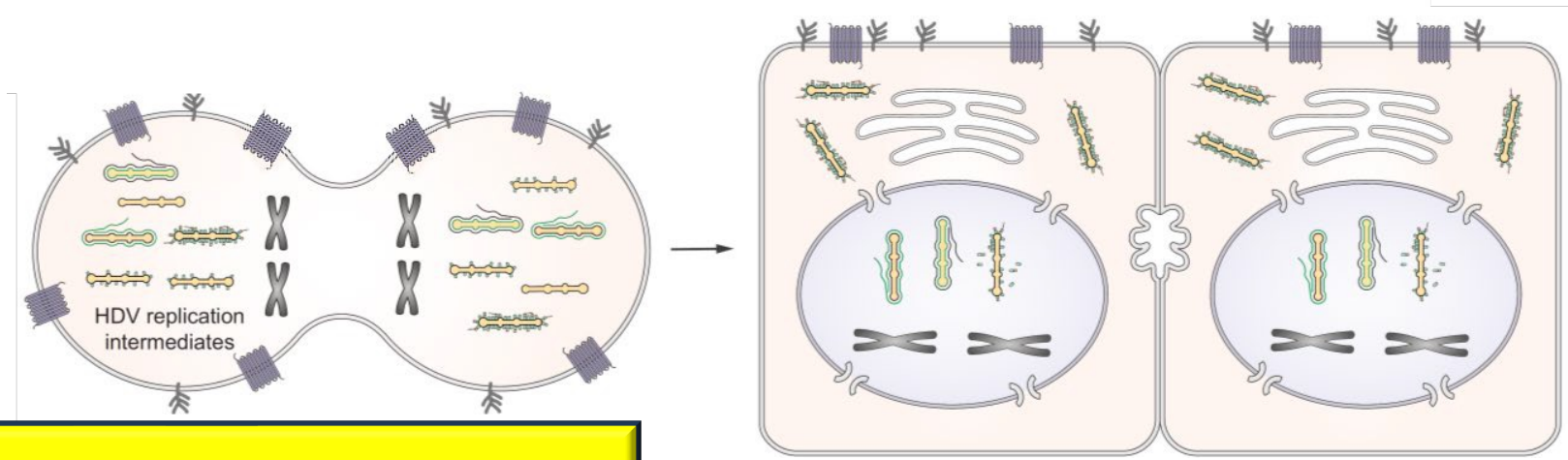
- Number of HDV infected cells (?)
- Intracellular HDV replication rate (Neither BLV nor IFN profoundly affect intracellular HDV replication, non-dividing cells may continue to produce/secrete HDV RNA)
- Number of liver cells susceptible of HDV infection (?)
- Efficiency of BLV-induced NTCP inhibition (probably high)
- Rates of cell-turnover of HDV infected cells (??)
- Mechanisms involved in cell deaths?
- HDV spreading mechanisms (NTCP-mediated vs NTCP-independent)
- Source of HBsAg – cccDNA vs integrated DNA (cccDNA is expected to be lost after mitosis, whereas integrated HBV DNA survives mitosis and leads to expansion of the HDV "replication space")

# HDV Life Cycle: Spreading and Propagation

**1) NTCP-mediated**
**(BLV-sensitive)**



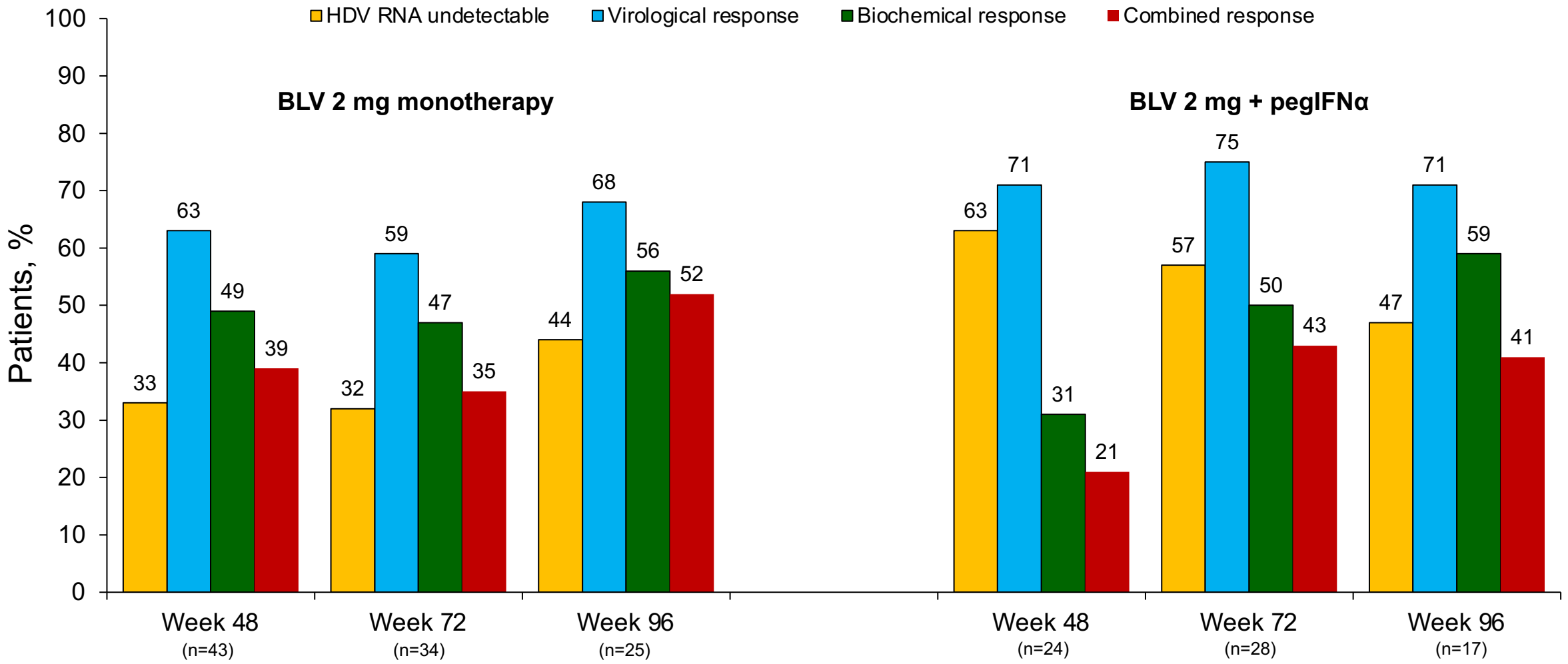

**2) Cell division-mediated**
**(NTCP independent)**
**(IFN-sensitive)**




**Which speading/propagation mechanism is predominant ?**

*Zhang Z, Urban S. J Hepatol. 2021; 74: 686–699*

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

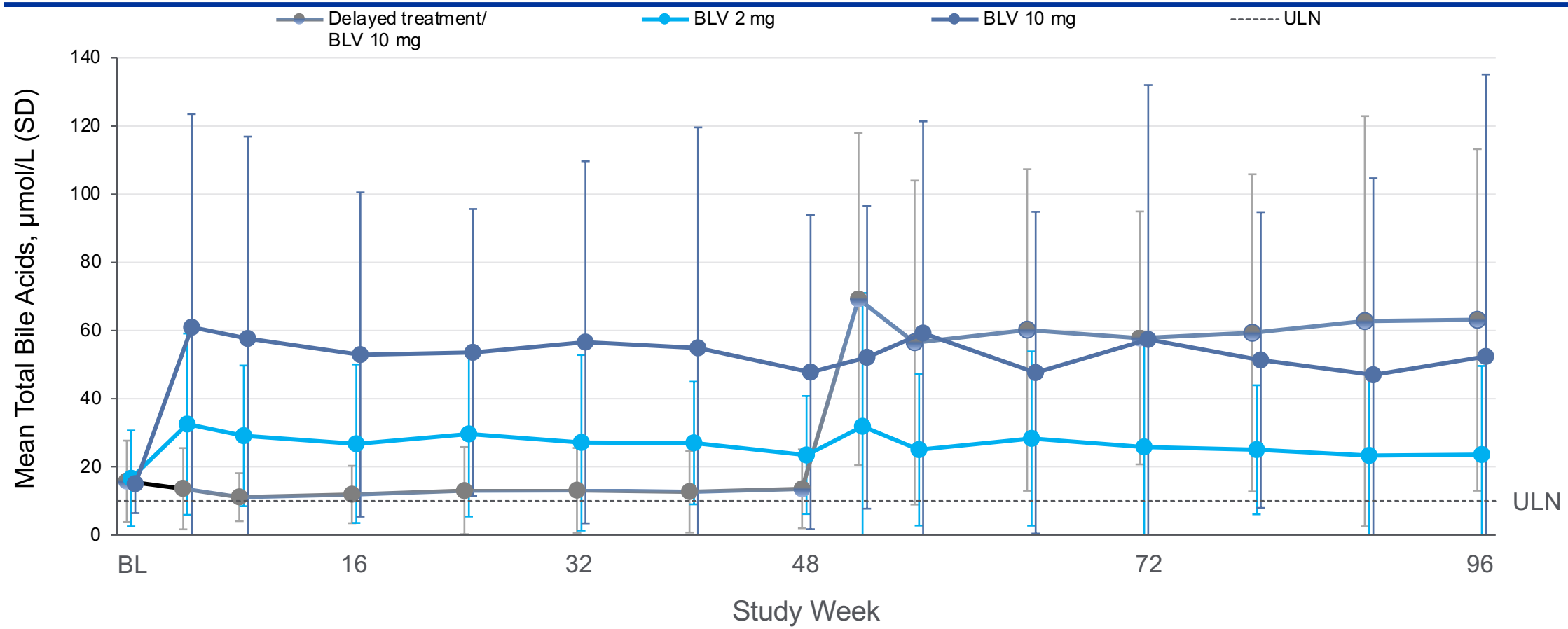



**Any role for BLV+Peg-IFN combined treatment ? Which strategy ?**
**See MYR203 and MYR204 trials**

**bined response**: virological and biochemical

*de Lédinghen V et al, AASLD 2022*

# 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

**Which are the long-term safety consequences of elevated serum BA?**
**Why the increase of BA levels is dose dependent but not efficacy?**

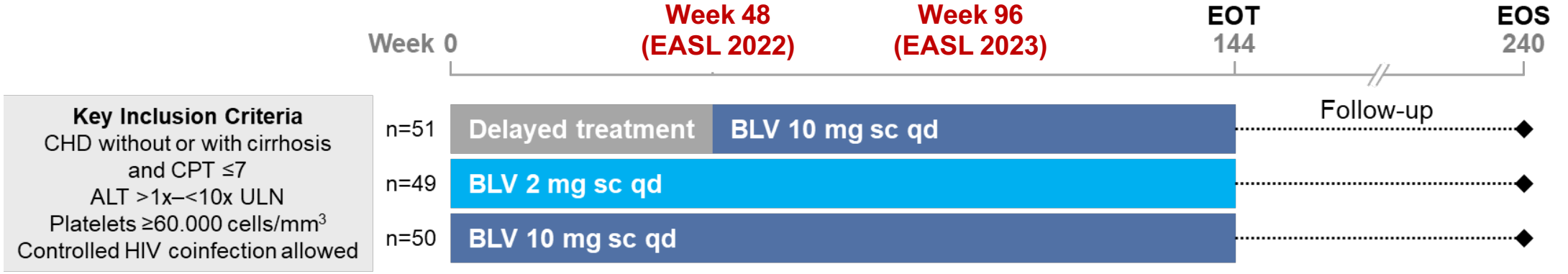
Wedemeyer H, et al. EASL 2023. Oral #OS-068

**Can we stop BLV monotherapy ?**

**Can we cure HDV infection without HBsAg loss ?**

# 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 $Log_{10}$ IU/mL from baseline and ALT normalization

BLV 10 mg, dosing not authorised for clinical use

## Week 96 Analysis Endpoints:

Proportion of patients with:

- HDV RNA decrease of ≥2 $Log_{10}$ IU/mL from baseline or undetectable HDV RNA
- Undetectable HDV RNA
- ALT normalization
- Change in liver stiffness
- Adverse Events

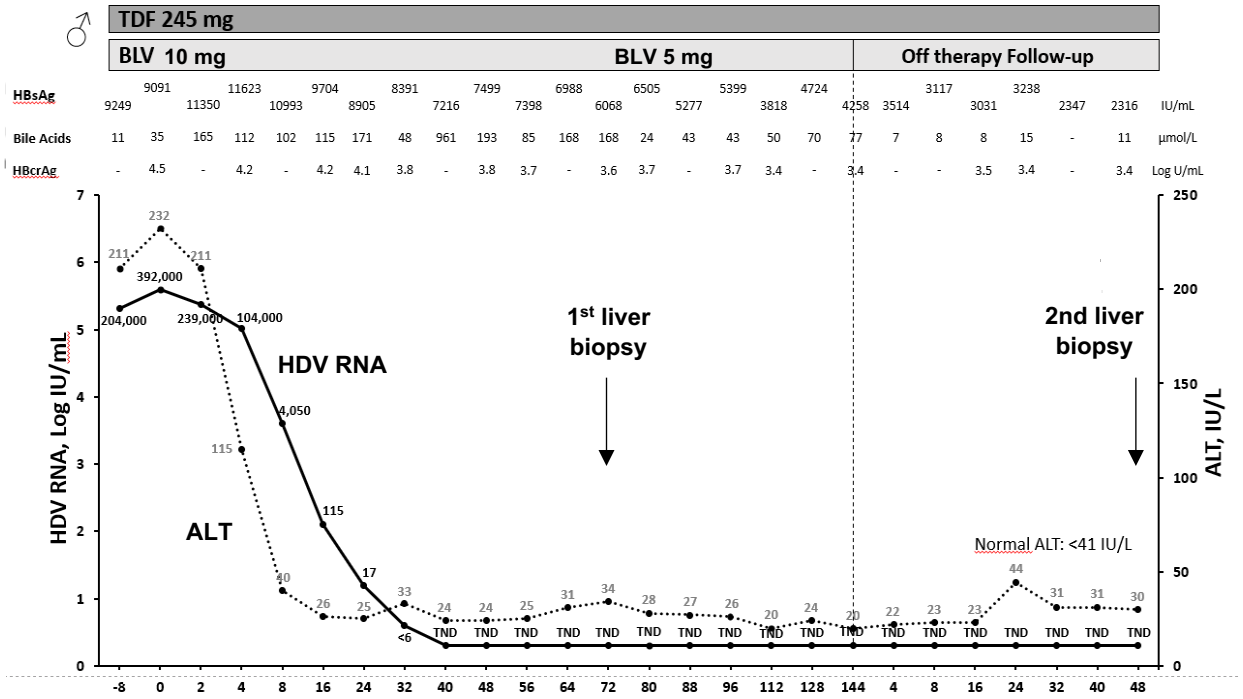
**Off-therapy results in 2025 ?**

*et al, NEJM 2023;389:22-32; Wedemeyer H et al, EASL 2023, Oral #068*

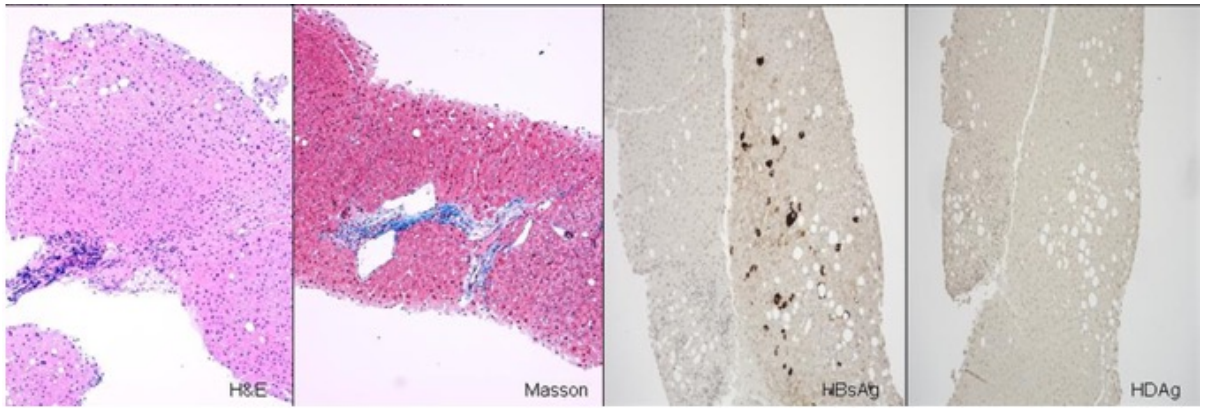
# The "Milan patient"
# A 3-year course of BLV monotherapy may cure HDV without HBsAs loss

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**

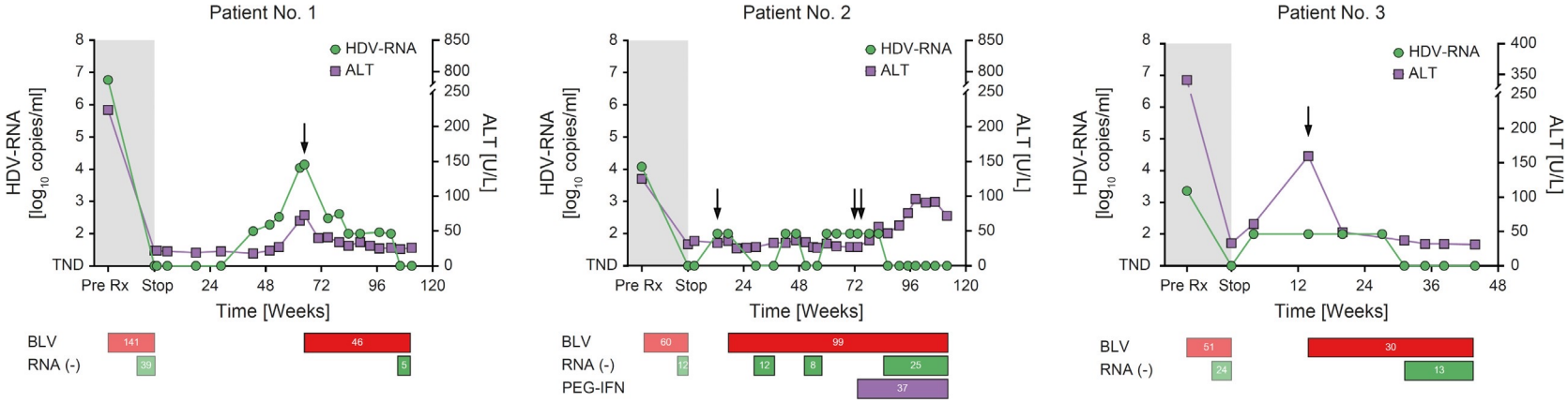
- **A 3-year course of BLV monotherapy may cure HDV infection even in difficult-to-treat patients with advanced compensated cirrhosis**
- **HDV eradication occurred without HBsAg loss**

**Can we stop BLV monotherapy after 2 years of full viral suppression (=TND)?**

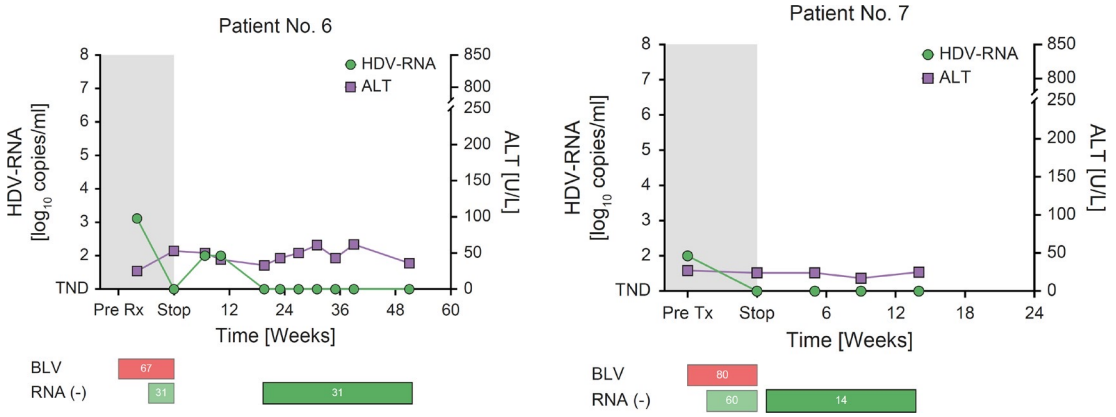
*Anolli MP et al, J Hepatol 2023*

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

## HDV 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*

# HBV Forum collaborative network
# Interpretation of HDV RNA levels according to lab report

| As example, we considered a putative assay with LoD=10 and LLoQ=100 IU/mL | | | |
|---|---|---|---|
| **HDV RNA levels** | **HDV RNA limits** | **HDV RNA interpretation** | **Comments** |
| Below LLoQ | < 100 IU/ml | Low positive viremia (below 100 IU/mL but not quantifiable, i.e., HDV RNA target detected [TD]), or negative for viremia (i.e., HDV RNA target not detected [TND]) | The LLoQ depends on the assay's performance characteristics. A result of below LLoQ includes both low level viremia and negative viremia test results |
| Below LoD | Interpreted as < 10 IU/ml | Low positive viremia (not quantifiable) or negative for viremia | Below LoD is not recognized by regulatory agencies as the assay cannot determine the concentration for samples < 100 IU/ml, i.e., the concentration could be < 10 IU/ml or between 10 and 100 IU/ml |
| TND | Undetectable | Undetectable | No virus (HDV RNA) detectable in sample (i.e., "negative"). This result is frequently/sometimes referred to HDV RNA <LLoQ TND |

HDV, hepatitis D virus; LLoQ, lower limit of quantitation; LoD, limit of detection; TD, target detected;



**Definition of «undetectable» HDVRNA differs across studies:**

- BLV trials: TND
- LNF trials: <LLOQ (<40 U)
- Real world BLV studies:
  - TND
  - <LOD (<6 units)
  - <LLOQ (<50-100 units)
  - <100 copies

**Gaps: different HDV RNA assays, different performances, different cutoffs, different reporting…..**

*Wedemeyer H et al, Hepatology 2023*

# Bulevirtide for HDV - 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. BLV is 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 in most patients but BLV can be successfully discontinued in some cases (few data)
- Combination with pegIFN in selected patients to be further explored (MYR204 at AASLD 23)
- However, many issues related to this new treatments need to be discussed…….

**How can we optimize the efficacy of BLV monotherapy ?**
**When can we stop BLV monotherapy ?**
**Which would be the best combination therapy to cure HDV ?**

# Thank You for Your Attention!

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