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HDV: il punto sulle nuove opzioni terapeutiche

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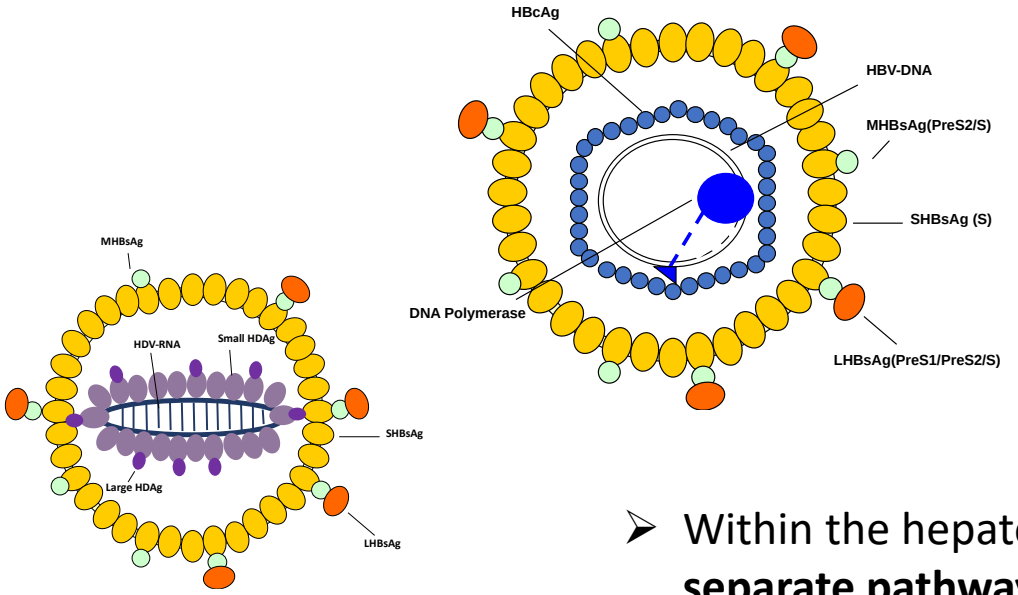
MR Brunetto **Disclosures**

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

HDV and HBV



- A florid **HDV infection** requires an ogoing HBV infection, as HDV uses **HBsAg** to **egress from** and **to re-enter** into hepatocytes

- Within the hepatocytes the **replicative circles** of **HBV** and **HDV** run completely **separate pathways** even if, in spite of being different for their genome (relaxed circular partially double stranded DNA for HBV and circular RNA for HDV), HBV and HDV are **both maintained** as **episomes** in the **nucleus** of infected cells and **use** the **cellular machinery** for **the transcription of their viral RNAs**

- **HDV persists** during **liver regeneration** and is **amplified** through cell division, mostly through clonal cell expansion, both in vitro and in vivo: HDV-RNA being trasmitted **to dividing cells even in the absence of HBV coinfection**

HDV clearance in absence of HBsAg loss appears highly unlikely

Rizzetto M et al, Infect Dis 1980; Cahng WS at al Virus Evol 2019; Lucifora et al, Antivial Research 2020; Giersch K , Gut 2019

Virologic endpoints inferred from IFN/Peg-IFN treatments

Endpoint	Parameter	Rate of occurrence with IFN treatment	Clinical benefit (improved survival)
Ideal	HBsAg loss	2.5% (0-25%)*	Yes§
Desirable	Undetectable HDV-RNA • 24 wPT • for 2 years after EOT • ≈ 8.9 years PT	29% (24-34%)* 50%** 36.6%***	Yes§,**,&
Acceptable	2 log HDV-RNA decline at EOT, maintained thereafter	n.a.**** 10/14 pts with normal ALT at EOT, maintained in 7/12 (58.3%) after 12 years	Yes****

Open Issues

- ✓ As HBsAg clearance occurs more frequently on long term follow-up, when should it be tested?
- ✓ Is the 24 wPT single point testing appropriate to define HDV-RNA undetectability?
- ✓ What about the 2 log decline according to the BL viremia levels?
- ✓ Is there a viremia threshold that correlates with HDV induced liver disease?

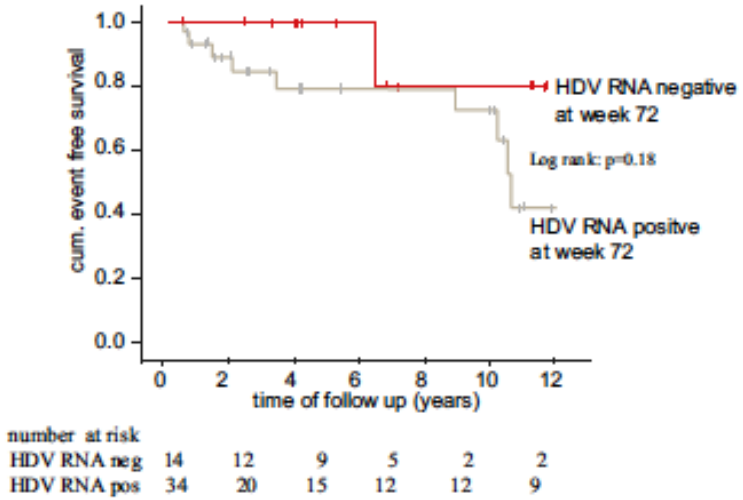
*Abdrakhman A et al Ant. Research 2021: Meta-Analysis on 13 and 8 studies using Peg-IFN ; ** Yurdaydin C et al J infct Diseases: 99 pts treated for at least 6 months, cumulative median duration 24 (6-126) months, median 2 courses; ***Wranke A et al JVH 2020: HIDIT I long term follow-up; **** Farci P et al Gastroenterology 2004: long term follow-up of 36 pts treated with standard IFN; § Heidrich B et al Hepatology 2014 and Wranke A et al Hepatology 2017; &Keskin O et al Clinical Gastroenterology and Hepatology 2015

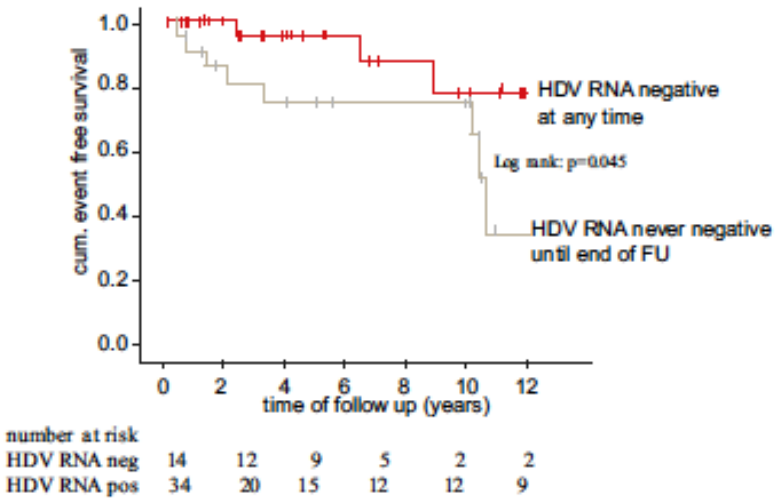
Ten years follow-up of a randomized controlled clinical trial in CHD

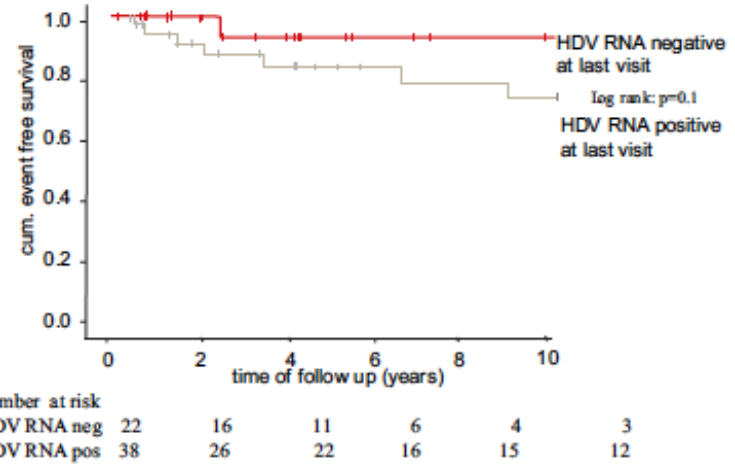
Wranke A et al JVH 2020

- **60** of the 90 pts enrolled in HIDIT I study had at least 1 visit beyond post-treatment week 24 - Median **follow-up 8.9** (1.6-13.4) years
- Treatments: 19/31 (61%) pts Peg-IFN+ADV, 20/29 (69%) pts Peg-IFN, 21/30 (70%) pts ADV; 19 pts were retreated with Peg-IFN
- **17 patients** developed **long-term complication** (associated with non response to treatment and baseline cirrhosis)
- **HDV-RNA detection:** in house quantitative assay on Cobas platform (**LOD 15 cp/ml → ~ 930 IU/ml**; Dynamic range $3x10^2$ -$5x10^8$ cp/ml)

Event-free survival according to viremia at different time points







At the last visit 22 (36.6%) pts had undetectable HDV-RNA (7 after a new Peg-IFN course), whereas 7 pts became negative during post-treatment fu.

- ✓ HDV-RNA response to Peg-IFN treatment predicted an improved long term clinical outcome
- ✓ Persistence of low HDV-RNA serum levels (~1000 IU/ml?), as it should be in patients with occasional HDV-RNA undetectability, appears associated with better clinical outcome

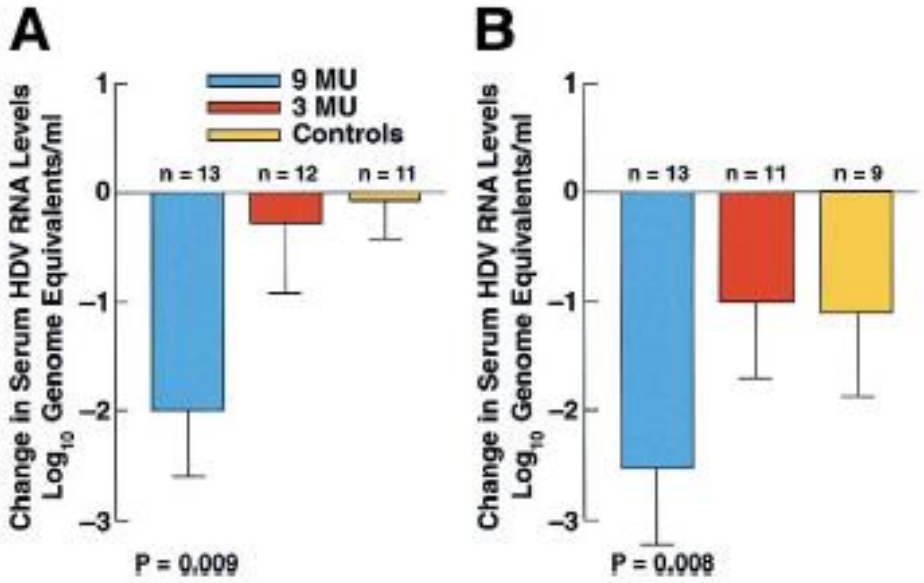
Long term benefits of IFN alpha therapy of CHD: regression of advanced hepatic fibrosis

- 2 to 14 years follow-up of 36 patients treated with 3/9 MU of IFN or untreated for 48 weeks
- Survival was significantly longer in high dose group than controls (p=0.003) or low dose group (p=0.019)

RT-PCR for HDV-RNA detection

- ✓ HDV-RNA was amplified by RT-PCR (primers derived from the carboxy-terminal portion of HDAg).
- ✓ The genome equivalent (1 g.eq=number of genomes present in the highest dilution that was positive in the RT-PCR).
- ✓ The genome equivalent titer was determined by testing 10-fold serial dilution of the extracted RNA

HDV-RNA decline from BL to EOT or EOF



- ✓ All the patients were HDV-RNA pos at EOT, but in high dose group viral load showed a significant decline from baseline (A), that was sustained thereafter (last evaluation, B) and 3 cleared viremia during f.u.
- ✓ **Viral load reduction** in high dose group **was associated with a dramatic improvement** in both grading (P=0.0004) and staging (P=0.007) of liver disease

Farci P et al, Gastroenterology 2004

Primary endpoints for clinical trials of new anti-HDV treatment

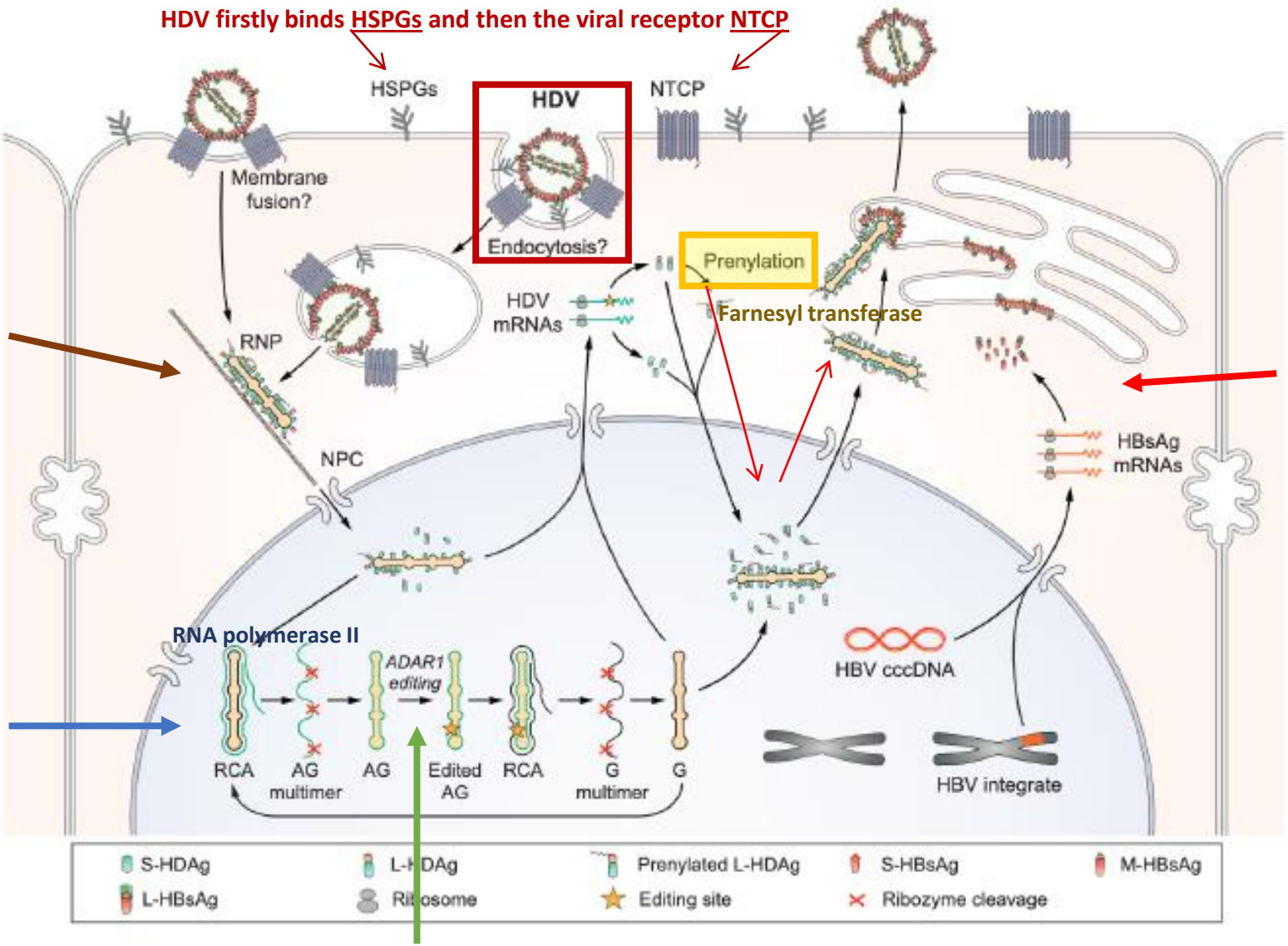
	Suppressive treatment	Finite treatment
FDA Developing drugs for CHD treatment (October 2019)	**Surrogate endpoint** likely to predict clinical benefit → **2 log reduction** in **HDV-RNA and ALT normalization** (acceptable)	**Undetectable HDV-RNA** and **ALT normalization** (the timing of assessment according to treatment strategy)
EASL-AASLD HBV treatment endpoints conference (March 2019)	**2 log reduction** in **HDV-RNA** might suffice	• **Undetectable** HDV-RNA **6 months** after stopping treatment • ALT normalisation (desired) • HBsAg loss (ideal)

- ✓ **Evidences** obtained with IFN/Peg-IFN treatment were **translated** in **different therapeutic settings** (suppressive vs finite; IFN vs Bulevirtide/Lonafarnib/etc..)
- ✓ **The weaker are the virologic endpoints, the more relevant become the other surrogate endpoints (biochemical …)**
- ✓ Accordingly, the **combined** (virological and biochemical) **endpoint** is used in the attempt to **predict** with **greater confidence** the **clinical benefit** of the ongoing antiviral treatment

FDA Developing Drugs for HDV. Available at:www.fda.gov/media/132137/download ; Report from the 2019 EASL-AASLD HBV treatment endopoints Conference

HDV replication cycle

HDV firstly binds HSPGs and then the viral receptor NTCP



Release of the RNP complex which is transported into the nucleus to initiate RNA replication

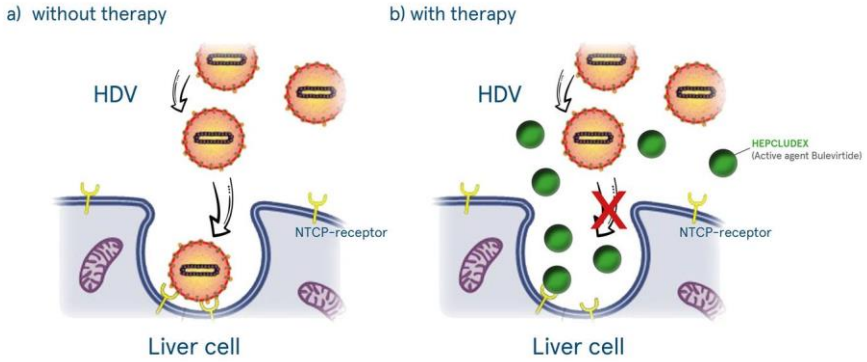
- Replication proceeds via a double rolling circle amplification mechanism, generating linear multimeric anti genomis and genomic RNAs, which are cleaved by 2 intrinsic rybozime
- The genomic RNA with negative polarity serves as the template for the first RCA step.

L-HDAg is responsible for RNP's interaction with the **HBV pre-S1 envelope proteins** which are expressed by cccDNA or integrated HBV DNA

During replication antigenomic is edited by adenosine deaminase acting of RNA1 (ADAR1)

Lucifora et al, Antivial Research 2020; Zhang Z et al J Hep 2021

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 are prevented and viral spread in the liver prevented.
- Proliferating virus-free hepatocytes should recolonize the liver, eliminating HBV ccc-DNA and hepatitis D

Administration:

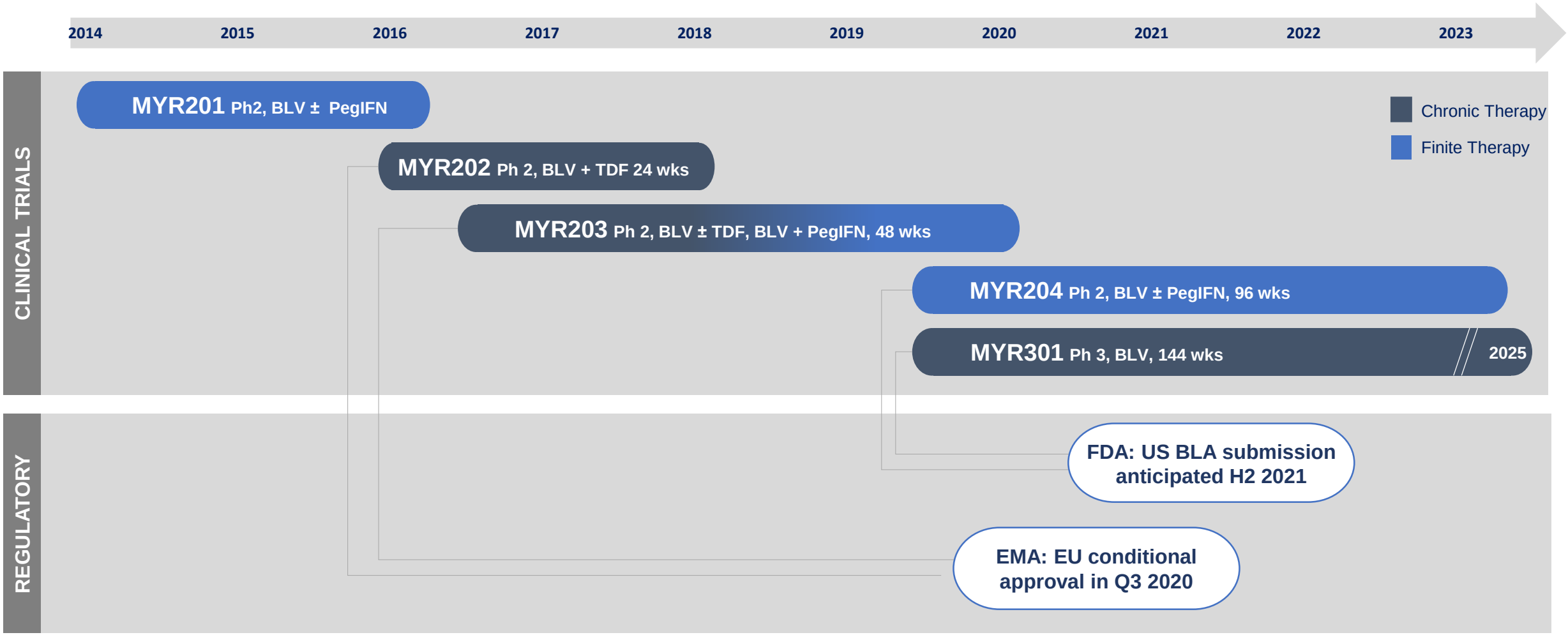
- Daily, self administered s.c injections

Approval

- **BLV** received a *'conditional authorisation' by EMA on July 2020 → drug available only in Europe and not in all Countries*
- This means that there is still **more evidence to come** about the medicine, which the **company is required to provide*.**
- BLV has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a **doctor experienced in the management of hepatitis D virus infection** (as described in section 4.2 of the SmPC)*.
- Since BLV has received a conditional authorisation, the company that **markets BLV** will **collect data on the use of the medicine in a patient registry** and will provide the final results from two ongoing studies*.

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

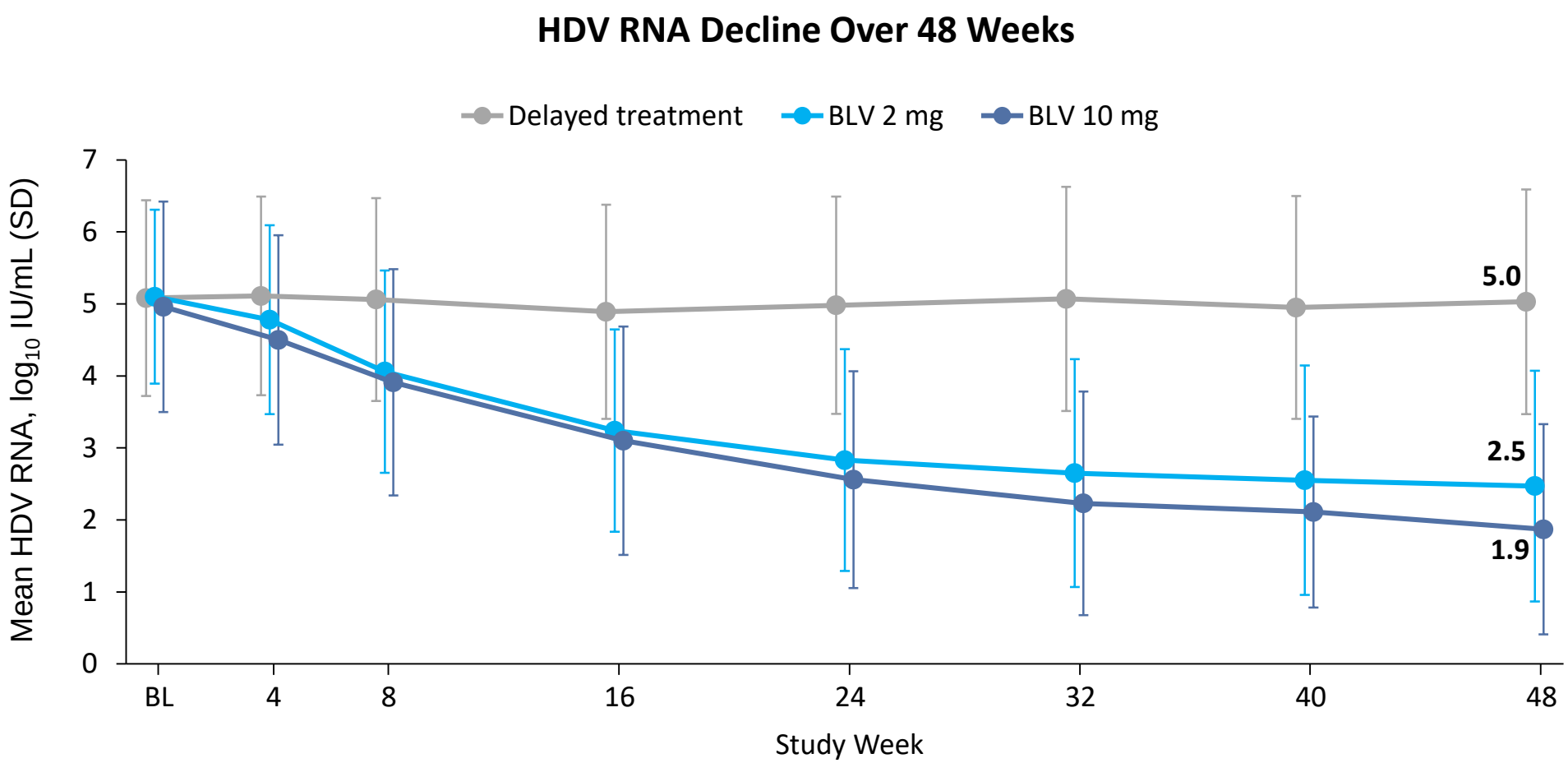
Entry inhibitor - Bulevirtide: Phase 2/3 Clinical Trial Program



FDA, Food and Drug Administration; PegIFN, pegylated interferon; TDF, tenofovir disoproxil fumarate; US, United States.

References: ClinicalTrials.gov. Study MYR201 (NCT02637999). Study MYR202 (NCT03546621). Study MYR203 (NCT02888106). Study MYR204 (NCT03852433). Study MYR301 (NCT03852719).

Efficacy and Safety of Bulevirtide Monotherapy 2 mg or 10 mg dose/daily for Treatment of CHD : Week 48 Primary Endpoint Results From a Phase 3 Randomized, Multicenter, Parallel Design Study

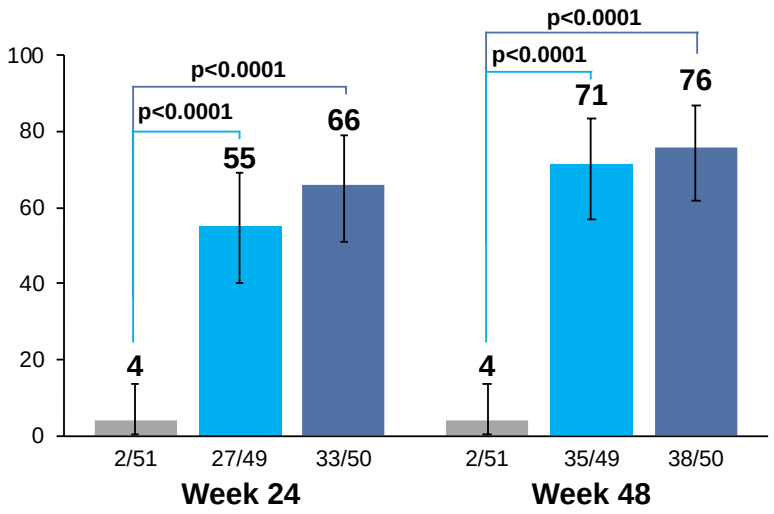


- ✓ Mean HDV RNA levels progressively declined to a similar degree over 48 weeks in both BLV groups
- ✓ **12% (2 mg BLV) and 20% (10 mg BLV) of the patients achieved undetectable HDV-RNA at week 48 (p=0.41)**

Wedemeyer H et al, ILC 2022

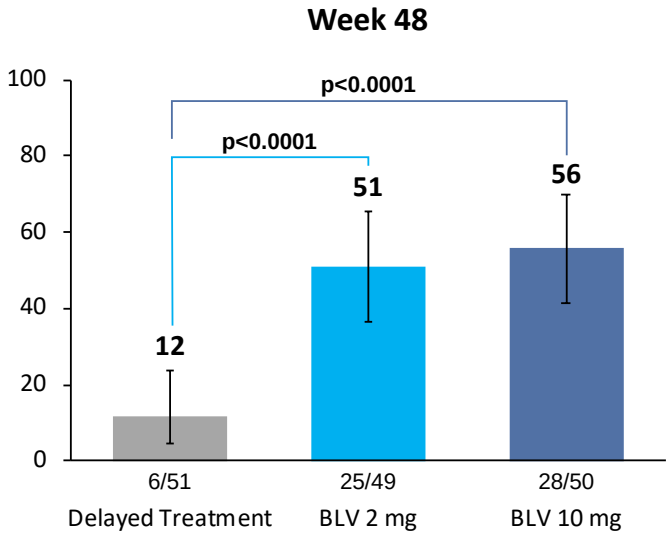
Efficacy and Safety of Bulevirtide Monotherapy 2 mg or 10 mg dose/daily for Treatment of CHD : Week 48 Primary Endpoint Results From a Phase 3 Randomized, Multicenter, Parallel Design Study

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

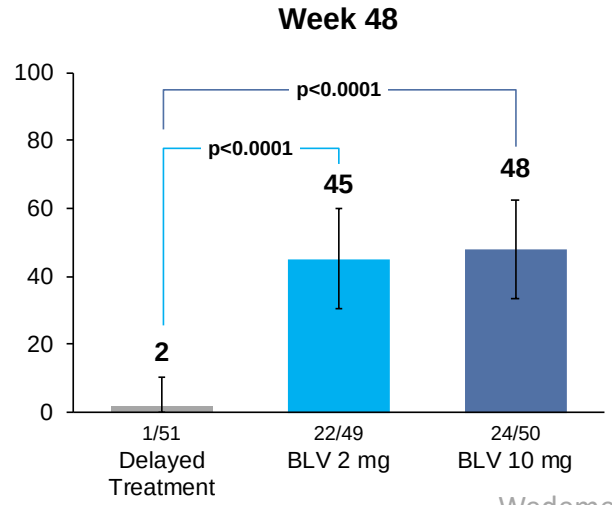


ALT Normalization at Weeks 24 and 48

Delayed treatment BLV 2 mg BLV 10 mg



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



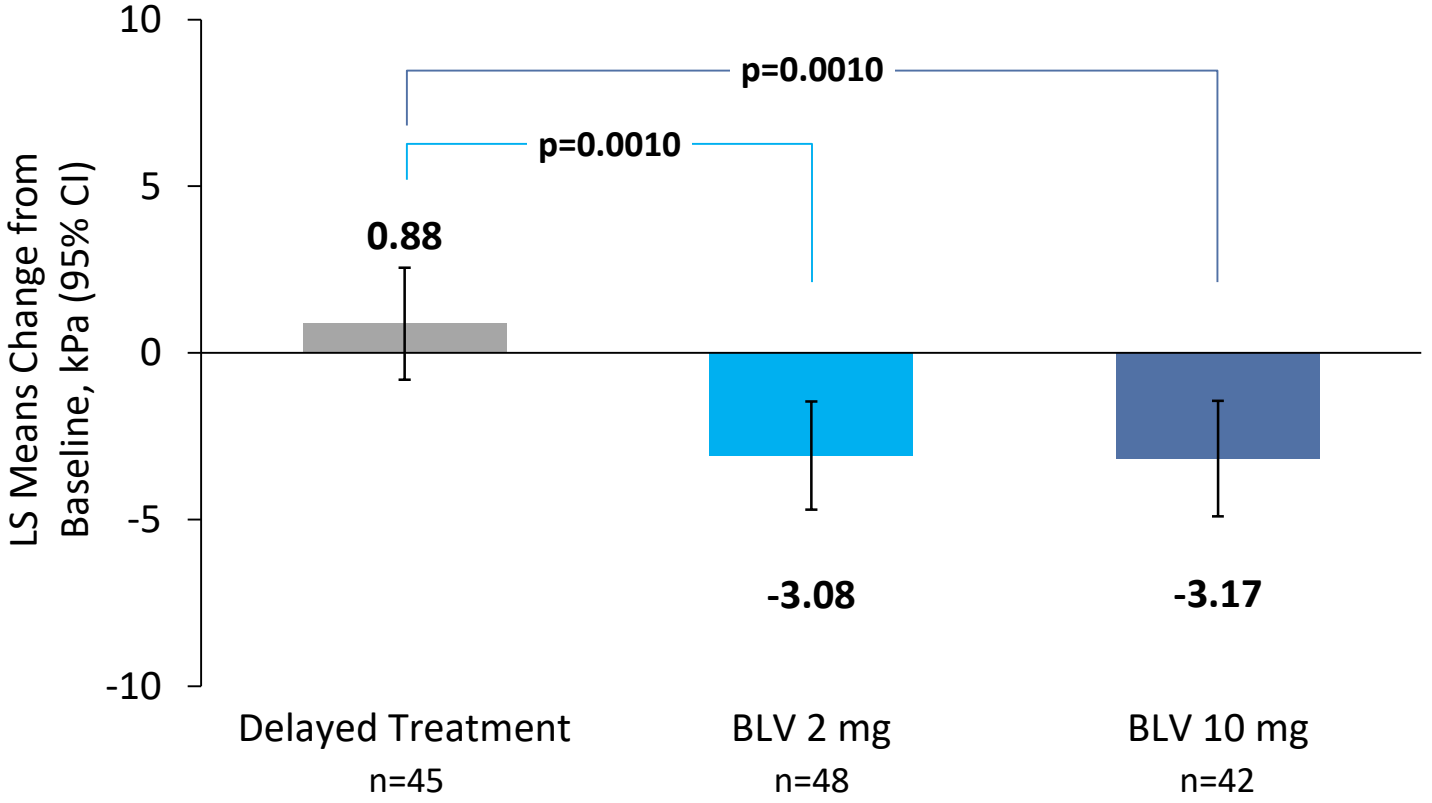
Wedemeyer H., ILC 2022

12% (2 mg BLV) and 20% (10 mg BLV) of the pts achieved undetectable HDV-RNA at week 48

- ✓ What about the 2 log decline according to the BL viremia levels?
- ✓ Is there a viremia threshold that correlates with HDV induced liver disease?

Individual data analysis correlating viremia kinetics with biochemical and histological data are required to appropriately define the virologic endpoints of CHD treatment

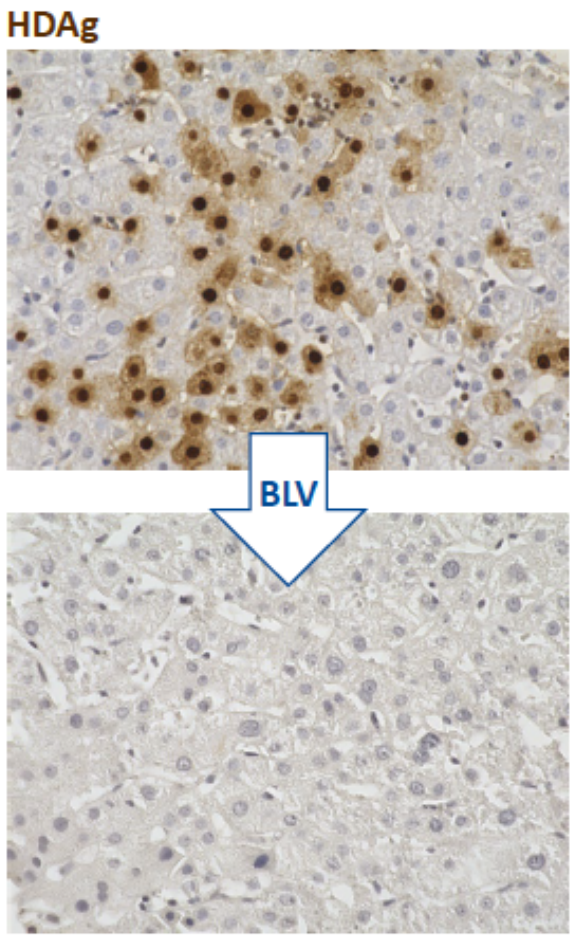
Change in Liver Stiffness at Week 48



- BLV was associated with significant reductions in liver stiffness by TE at both dose levels vs delayed treatment

Wedemeyer H et al, ILC 2022

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



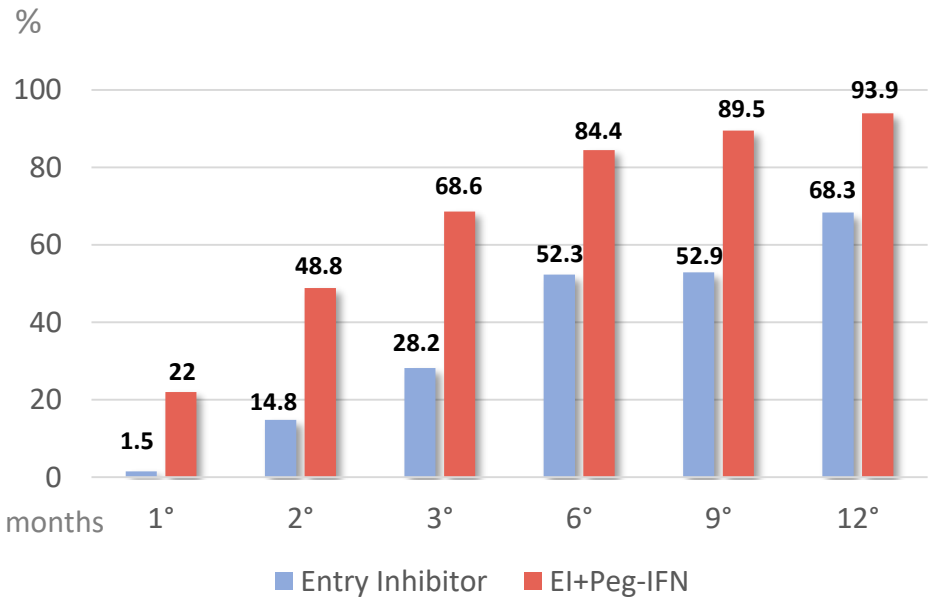
- Intrahepatic levels of HDV RNA strongly declined (>2 Log10) after 48 weeks of BLV treatment, reaching undetectable HDV RNA in 37% (2 mg) and 62% (10 mg) of patients. The results from the two trials (MYR202 and MYR203) were consistent.
- The number of HDAg+ hepatocytes strongly declined (2 Log10) reaching 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.

Allweiss L et al, Molecular biology of HBV, Paris 2022

Safety and Efficacy of 2 mg Bulevirtide in Chronic HBV/HDV Co-Infection: the French Early Access Program

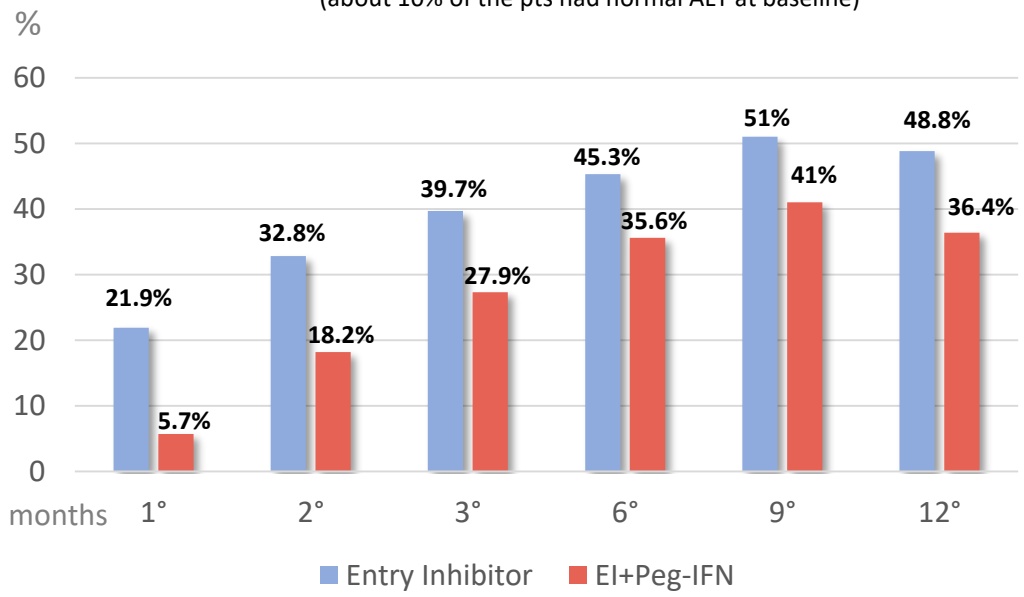
- 145 adults with compensated cirrhosis or severe liver fibrosis (F3) or with F2 fibrosis with persistent ALT >2 x ULN for ≥6 mo (N = 145) were enrolled in a multicenter, observational study;
- 77 received entry inhibitor (2 mg) monotherapy and 68 entry inhibitor (2 mg) + Peg-IFN

HDV-RNA decline ≥ 2log or undetectable



ALT < 40 IU/l

(about 10% of the pts had normal ALT at baseline)



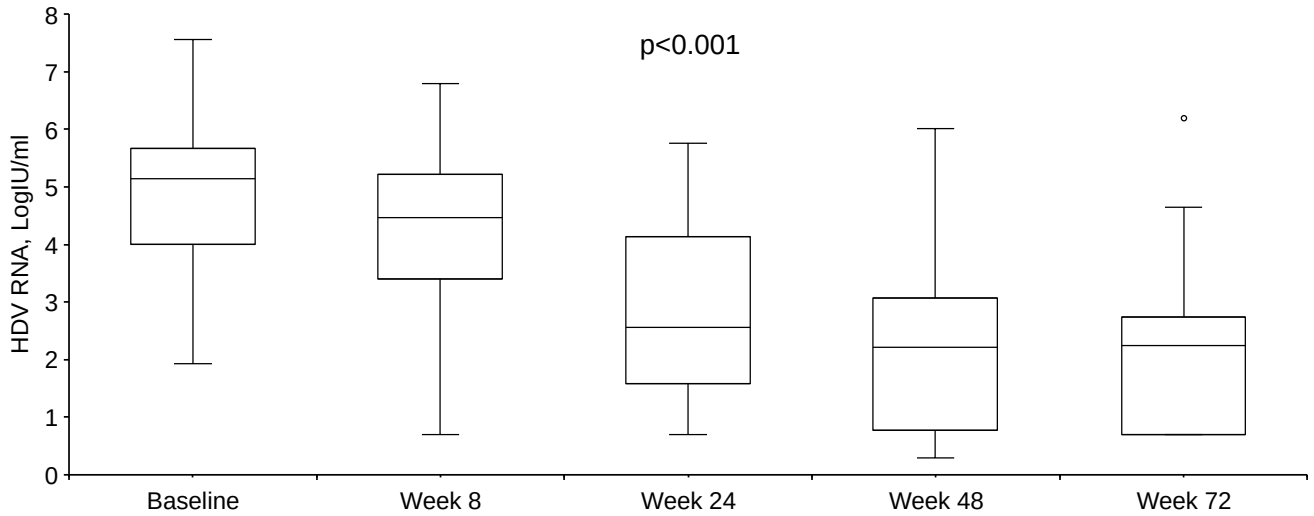
Entry inhibitor monotherapy was associated with a slower HDV-RNA decline as compared to Combo therapy, as expected the opposite occurred for ALT

De Ledinghen. AASLD 2021. Abstr OA21.

Extension of Bulevirtide Monotherapy to 72 Weeks in HDV Patients with Compensated Cirrhosis: Efficacy and Safety From the Italian Multicenter Study (HEP4Di) - Interim Analysis

- Retrospective, multicenter, investigator-driven, real-world
- Enrollment Period:December 2020 – May 2022
- Enrolling Centers: 16 Italian Centers
- **93 cirrhotic patients (35% Child A6; 55% with varices; LSM, kPa 17.4 (4.7-68.1)**

HDV-RNA decline



	Baseline	Week 8	Week 24	Week 48	Week 72
Median Range	5.2 (1.9-7.6)	4.5 (0.7-6.8)	2.6 (0.7-5.6)	2.2 (0.7-6.0)	2.3 (0.7-6.2)
HDV RNA Decline (Log)			**2.3 (0.5-4.1)**	**3.0 (0.2-4.1)**	**2.8 (0.1-5.3)**
Virological response (≥2 Log decline or TND)	**8%**		**67%**	**77%**	**75%**

- **3 pts with < 1 log decline at week 24**
- **Combined response 45% of the patients at week 24, 63% at week 72**
- **Liver Stifness: BL 21.8 (7.8-68.1) - week 24 17.3 (6.3-51.9) kPa, p=0.04 (in 22 pts); 16.5 (6.2-40.4) kPa in 18 pts**

Degasperi E et al, AASLD 2022

- Is there a HDV-RNA threshold that correlates with HDV induced liver damage?
- In some patients the ALT and HDV-RNA kinetics are dissociated: which are the underlying mechanisms?
- Which are the HDV-RNA kinetics on log term treatment? Any rebound while patients are still on treatment?
- Can BLV monotherapy achieve the clearance of HDV infection?

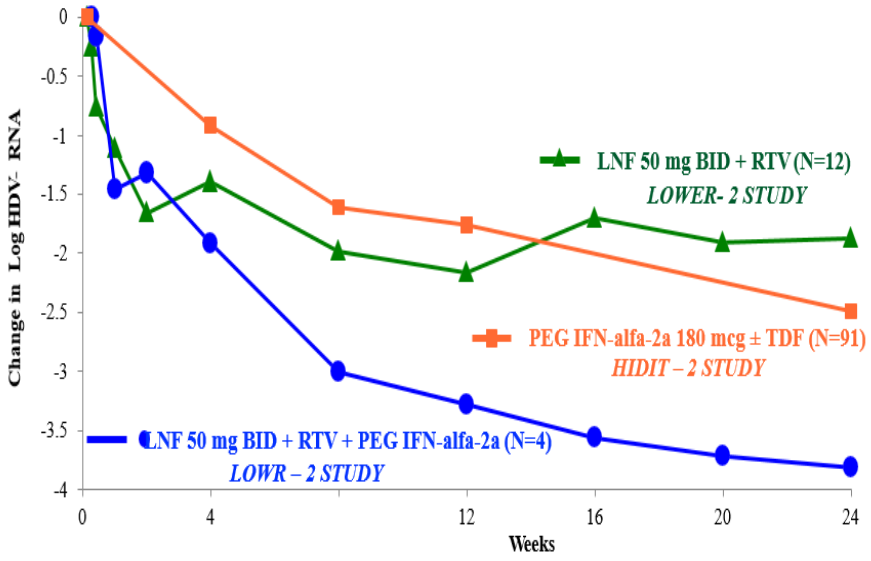
Magritte R, Le retour, 1940

Lonafarnib (LNF)

- LNF is an **oral inhibitor of Farnesyl transferase**, an enzyme involved in the **modification of proteins** through a process called **prenylation**
- Originally, LNF was developed as **inhibitor of farnesylation of RAS proteins**, that mediates oncogenic transformation of cells
- Development abandoned due to low efficacy (evasion by oncogenic RAS)
- Prenylation of HDAg promotes its association with HBsAg and is essential for initiating the HDV particle formation process

Proposed mechanisms contributing to the antiviral activity of LNF

1. Direct inhibition of farnesylation of large HDAg blocking the assembly and release of HDV
2. Not secreted large HDAg exerts its transdominant effect on HDV-RNA replication
3. Intracellular retention of large HDAg induces innate immune responses in HDV infected cultured cells

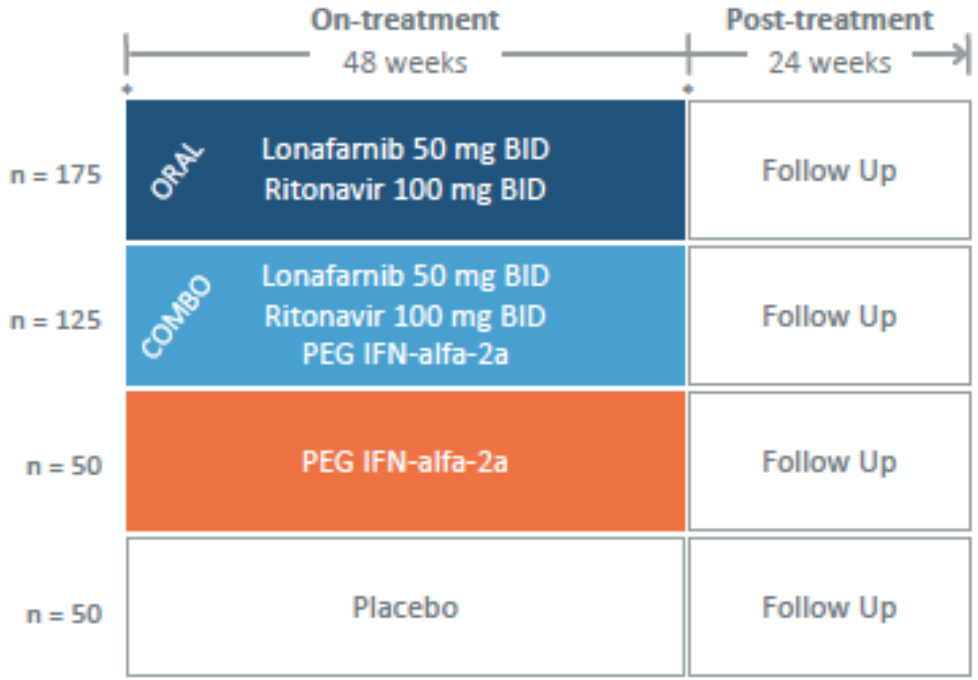


- **All-oral:** Lonafarnib boosted with Ritonavir
  - 46% (6 of 13) patients ≥ 2 log decline or BLQ at Week 24
  - 60% patients normalized ALT at Week 24
- **Combination:** Lonafarnib boosted RTV+PEG IFN-alfa2a
  - 89% (8 of 9) patients ≥ 2 log decline or BLQ at Week 24
  - 78% patients normalized ALT at Week 24
- **Safety:** Predominant AEs for LNF were GI-related (mild/mod.)

Elazar M et al in Hepatitis D, by Rizzetto M 2019; Wiliams et al J Gen Virol 2009;; Glenn JS et al J Virol 1991; Yurdaydin C et al, Hepatology 2021

Phase 3 D-LIVR Week 48 Topline Data December 8,2022

D-LIVR Phase 3 Global Study



Contribution of effect only

Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

Secondary Endpoint at Week 48

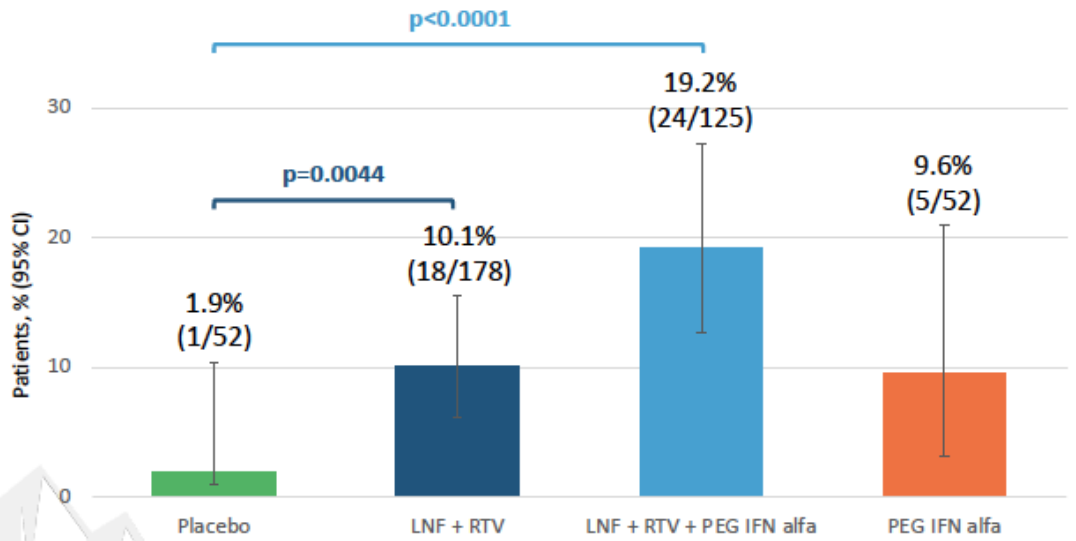
No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

* Liver biopsy
All patients will be maintained on background HBV nucleoside therapy.

Phase 3 D-LIVR Week 48 Topline Data
December 8,2022

Primary Endpoint Achieved with Significance in BOTH Arms

% PATIENTS ACHIEVING COMPOSITE ≥2 LOG DECLINE IN HDV RNA + ALT NORMALIZATION AT WEEK 48



Histology Response Rates at Week 48

PATIENTS WITH EVALUABLE PAIRED BIOPSIES (n=229)

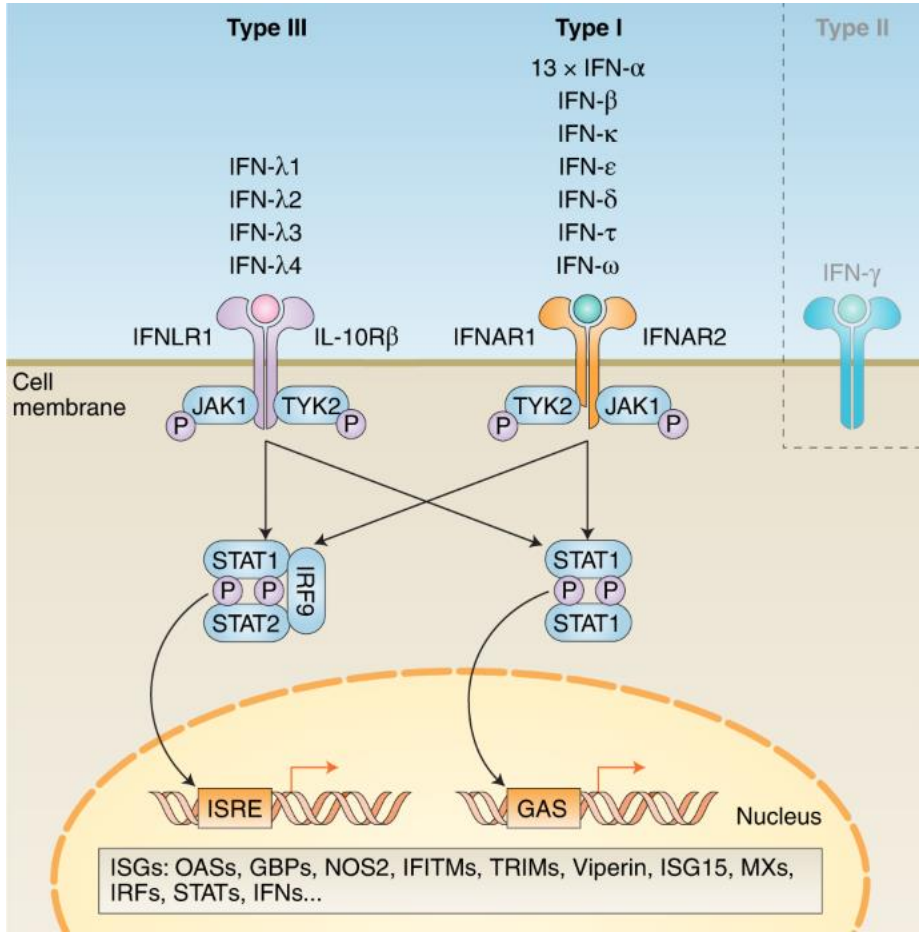
	% (n)			
Response	Oral n=107	Combo n=66	PEG IFN alfa n=26	Placebo n=30
Histologic Composite Endpoint	33% (35) (p=0.61)	53% (35) (p=0.0139)	38% (10) (p=0.46)	27% (8)

- Histologic Composite Endpoint: ≥ 2-point improvement in HAI* score + no worsening in Ishak fibrosis score
- Liver histology is the most direct way to assess improvements in:
  - Liver injury (necrosis and inflammation) measured by HAI score
  - Liver scarring (fibrosis) measured by fibrosis score

- **33% of patients dose reduced**
- **50% subsequently dose increased**

Lambda - Interferon

- The type I IFN receptor is expressed in almost all cell types.
- The type III IFN receptor (IFNLR1/IL10RB complex) is expressed primarily in cells of epithelial origin and few immune cells (mainly neutrophils and subsets of dendritic cells, DCs), conferring selective IFNλ responsiveness to them.



Phase II study

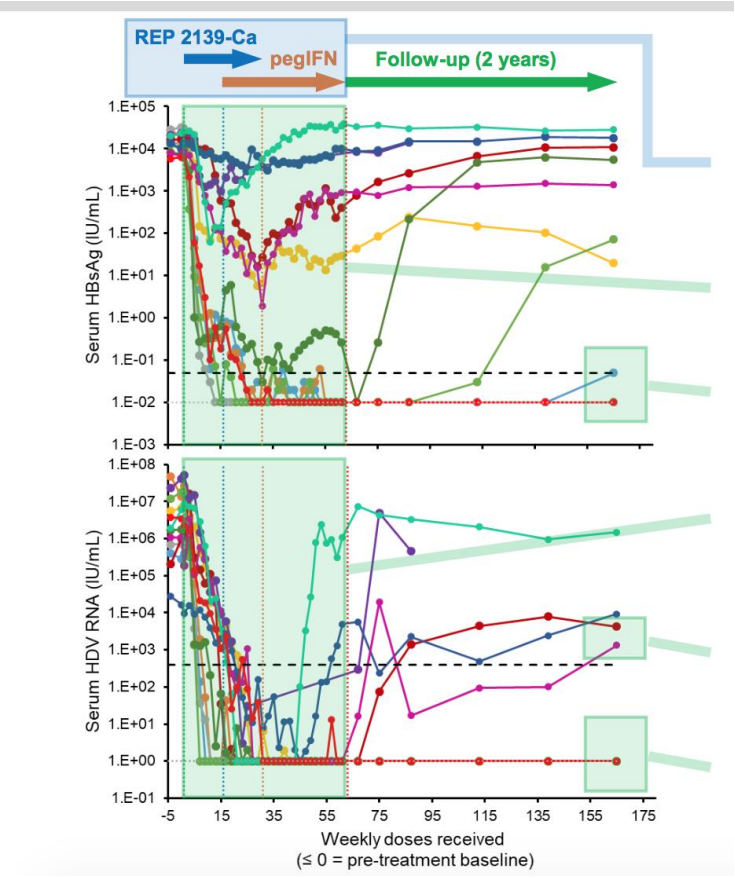
- 33 CHD pts treated with 180 or 120 ug/w fro 48 w
- EOT 2 log HDV-RNA declined observed in **50%** (7/14) and 21% (4/19) of treated pts
- **36%** (4/14) pts treated with 180 ug/w had undetectable HDV-RNA at w 24
- **AE**: **hyperbilirubinemia** and **elevated ALT**

IFN λ was also given in **combination** with **Lonafarnib** for 24 weeks: **50%** of the pts had undetectable HDV-RNA at EOT and **23%** maintained the response 24 w posttreatment discontinuation

Etzion O et al Jhep 2019

REP 2139 Ca + PEG-IFN alfa: two years follow-up of 12 HBeAg–neg. patients with chronic HBV/HDV

12 CHD pts received 500 mg REP2139 iv/once weekly for 15 weeks, followed by additional 15 week of 250 mg REP2130 in combination with Peg-IFN followed by Peg-IFN monotherapy for 33 weeks.



Bazinet et al., Lancet Gastroenter Hepatol 2017

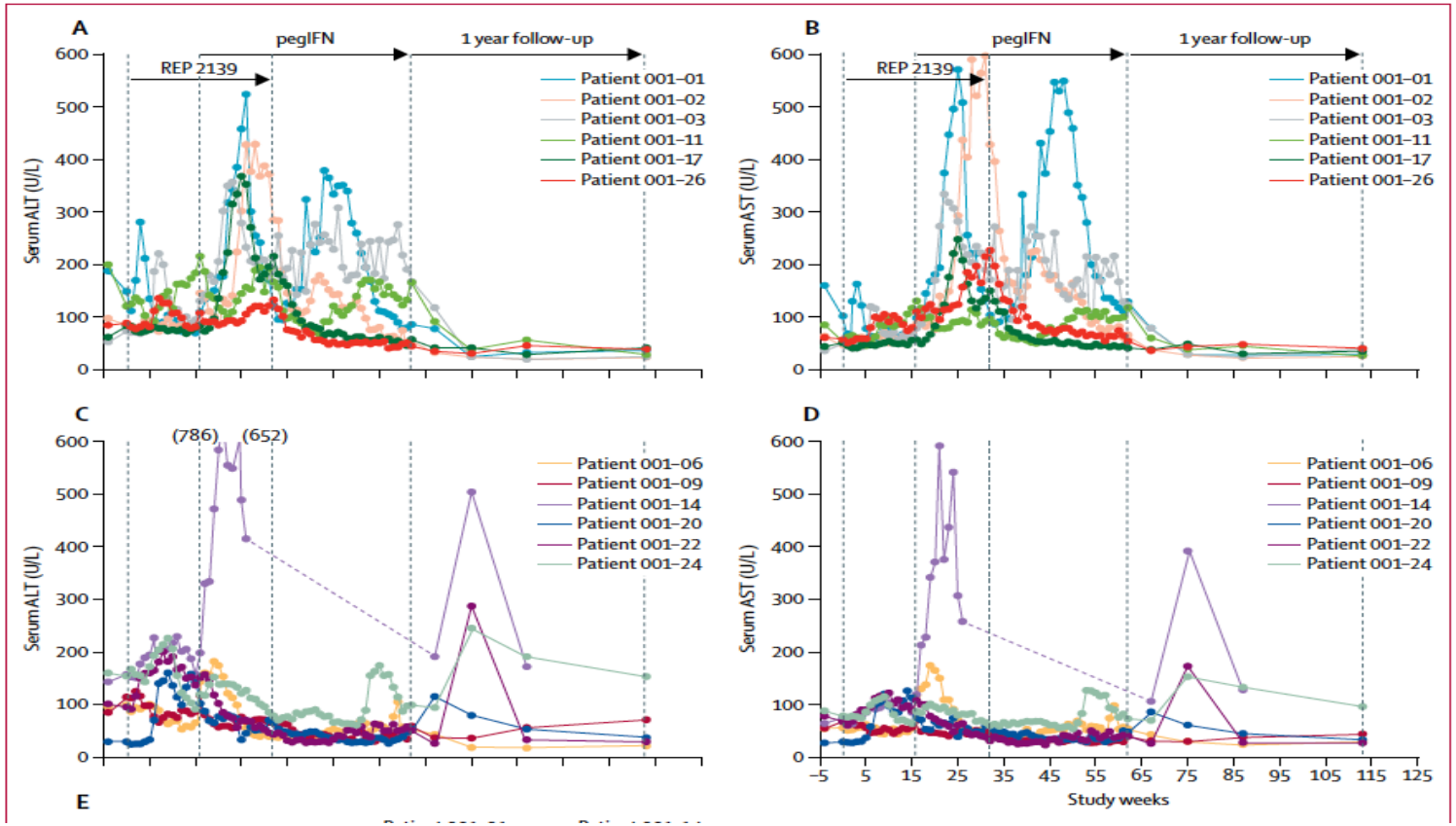
HBsAg

- *on therapy* decline was reported in 8/12 (66.6%), with HBsAg loss at EOT in 6//12 (50%)
- *1 year post treatment follow-up: undetectbale* HBsAg in 5/12 (42%)

HDV RNA

- *on therapy* decline > 5 log in all, 75% (9/12) achieved undetectbale HDV-RNA
- *1 year post treatment follow -up:* 7/11 (64%) maintained undetectable HDV-RNA

Safety and Efficacy of REP 2139 and Peg-IFN for treatment naive patients with CHD and HDV co-infection (REP 301 and REP 301-LFT): a non randomized, open label, Phase 2 trial



Patients with HBsAg < 1 IU/ml at the time of Peg-IFN start

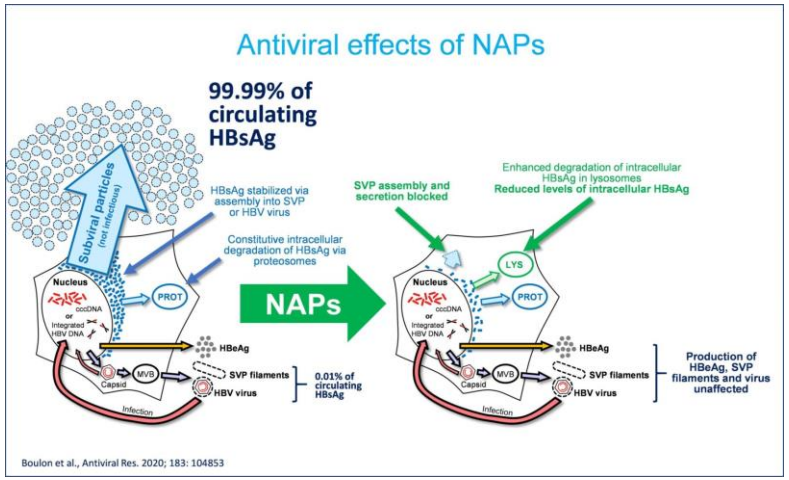
Patients with HBsAg > 1 IU/ml at the time of Peg-IFN start

ALT flares occurred mainly in patients with HBsAg serum levels < 1 IU/ml at the time of Peg-IFN start and were associated with profound increases of anti-HBs and correlated with the maintenance of functional control of HBV and HDV at 1 year f.u.

Bazinet M et al, Lancet Gastor-Hep 2017

HBsAg as a target

NAPs

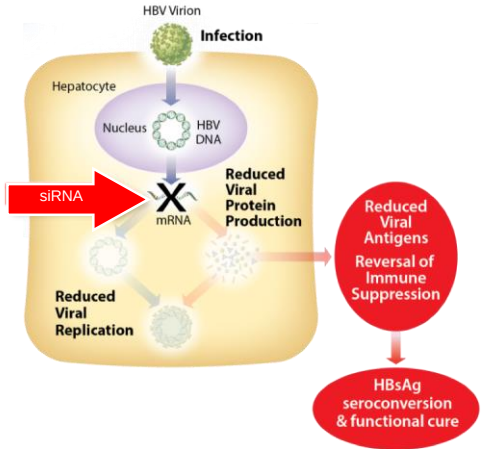


REP-2139, a negatively charged molecules made up of single stranded phosphorotioated oligonucleotides, selectively destabilize Subviral Particles (SVP) assembly and/or secretion and leads also to an increased degradation of intracellular HBsAg by the lysosomal pathaway

64% of 11 pts maintained undetectable HDV-RNA 3.5 years after treatment discontinuation
36% undetectbale HBsAg

Bazinet M et al Hepatol Comm. 2021

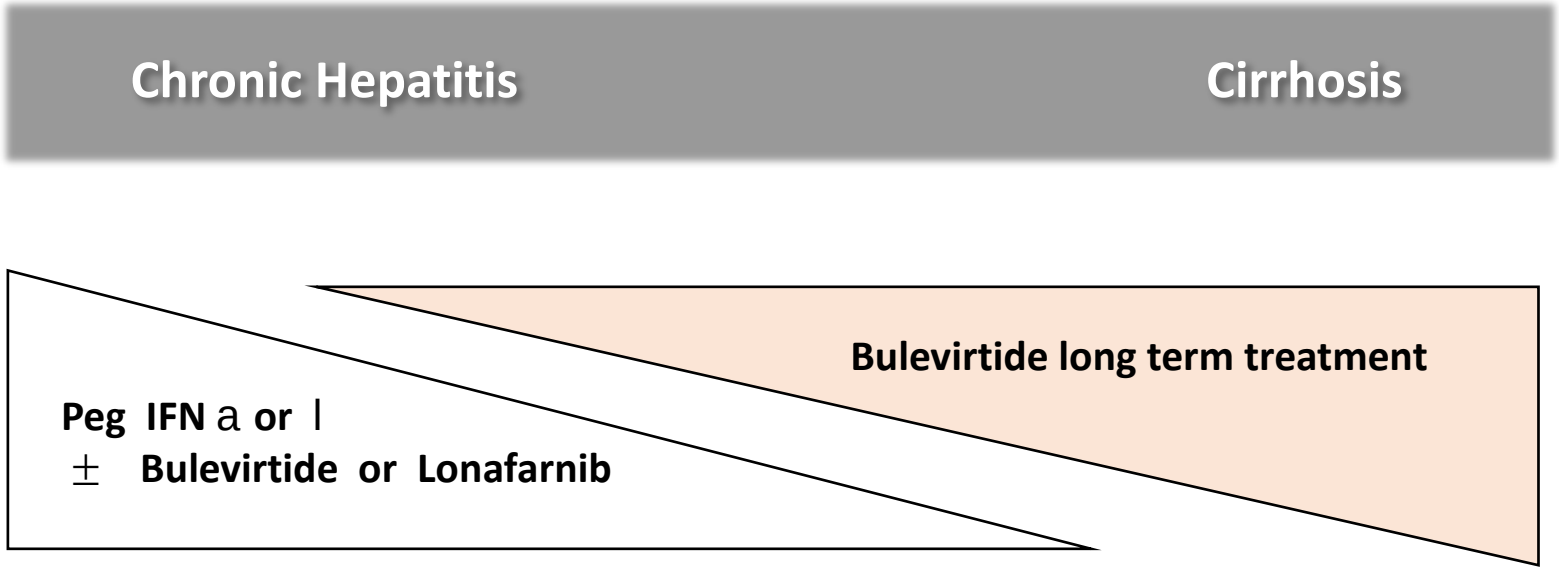
siRNA



JNJ-3989 and VIR-2218 (siRNA) target all HBV RNAs, reducing levels of all viral proteins, including HBsAg

siRNA (JNJ-3989, VIR-2218) in combination with NA +/- other molecules interfering with viral entry (i.e VIR-3434) are under investigation in CHD

Chronic Hepatitis D



To cure the infection/disease **To control the infection/disease**

Additional factors influencing the treatment schedule:

- ✓ Extent of HDV replication
- ✓ Phase of HBV infection (HBeAg/anti-HBe status; HBV-DNA and HBsAg levels)

Brunetto MR, Personal Opinion 2022