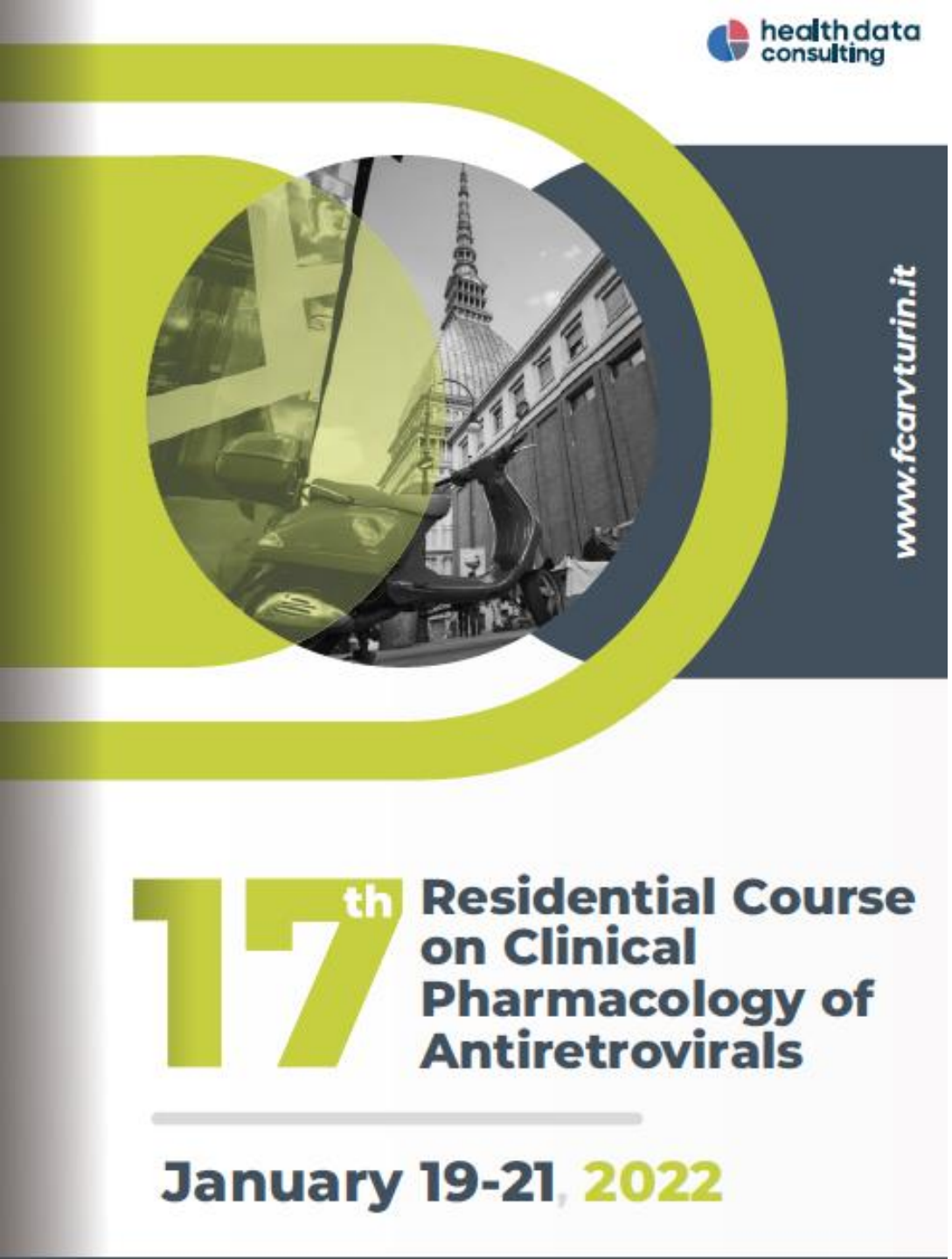

Novel targets and strategies to cure HBV

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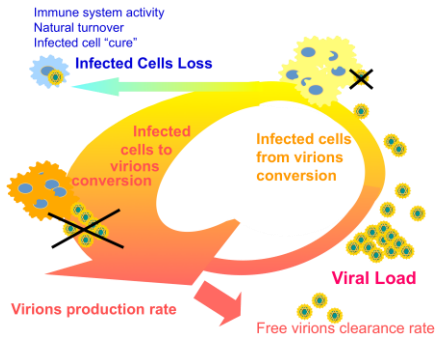
DAI Specialità mediche - UO Epatologia – Azienda Ospedaliero Universitaria Pisana - Centro Riferimento Regionale *"Diagnosi e trattamento delle epatopatie croniche e del tumore di fegato"*

Response to antiviral treatment: how it is changing the way to look at it



Virological responses

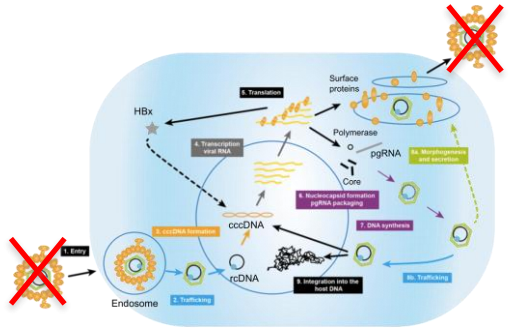
- *during NA* **undetectable HBV DNA** by a sensitive PCR (LoD 10 IU/ml)
- *after NA*, sustained off-therapy virological response, **HBV DNA <2,000 IU/ml** for at least 12 months
- *during PegIFNa* **HBV DNA <2,000 IU/ml** at 6 months and at the end of therapy.
- *after PegIFNa* **HBV DNA <2,000 IU/ml** for at least12 months

Serological responses

- **HBeAg** are HBeAg loss and HBeAg seroconversion
- **HBsAg** are HBsAg loss and HBsAg seroconversion

On or off therapy

EASL, HBV CPG 2017



Complete sterilising cure:
undetectable serum **HBsAg** and **eradication of HBV-DNA** including intrahepatic cccDNA and integrated HBV-DNA

Functional cure:
sustained, **undetectable** serum **HBsAg** and **HBV-DNA** with/without seroconversion to anti-HBs *(several levels of functional cure according to cccDNA status: complete shut down of cccDNA transcription or its elimination)*

Partial cure:
detectable serum HBsAg, but **persistently undetectable** serum **HBV-DNA**

Off therapy

Cornberg M et aJ Hep 2020 *Guidance for design and endpoints of clinical trials in CHB – Report from 2019 EASL-AASLD HBV treatment endpoints Conference*

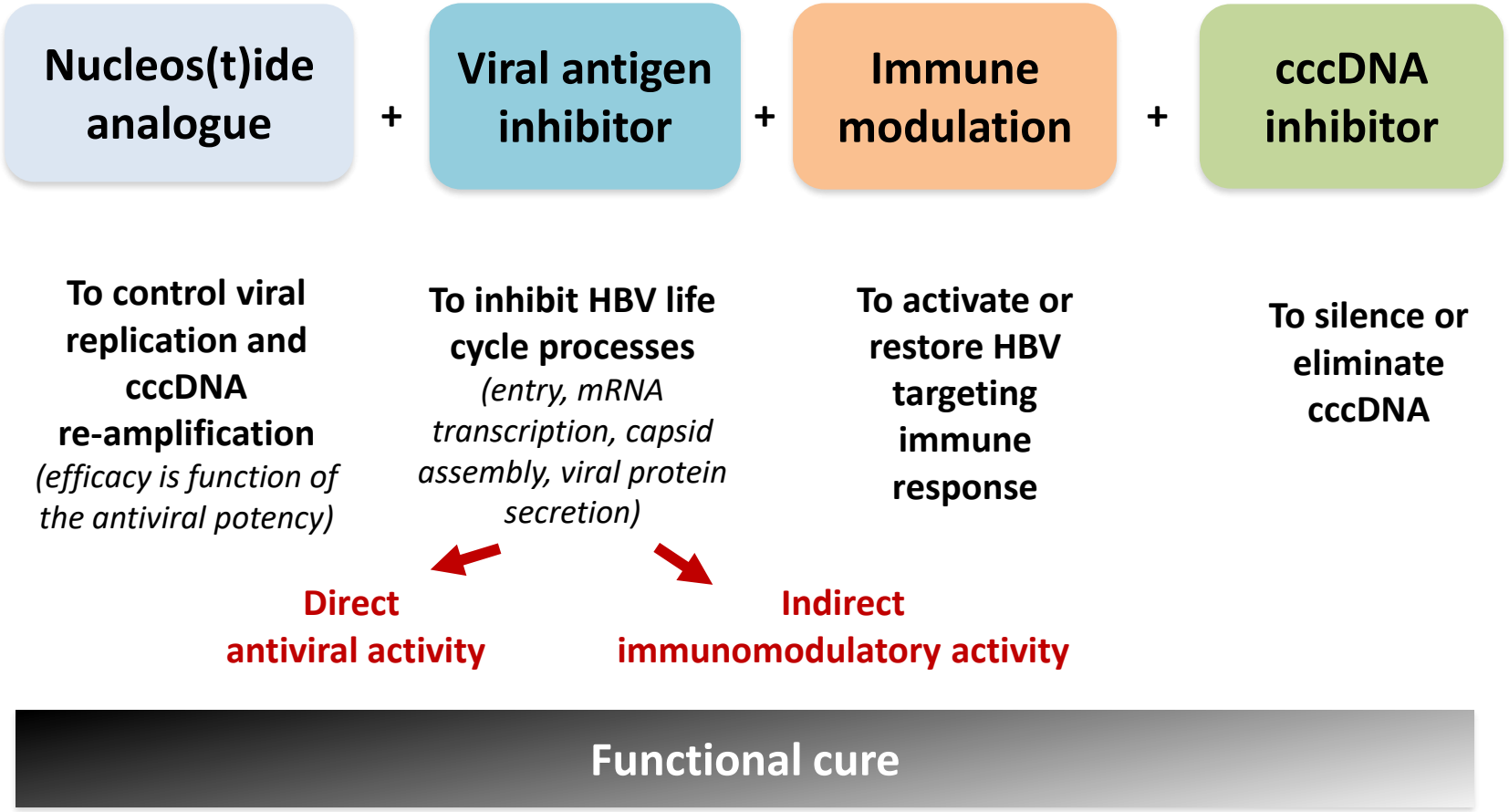
Towards a functional cure of chronic Hepatitis B

- In spite of **promising preliminary** data as far as target engagement, inhibition of viral proteins, pgRNA and HBV-DNA production, we are still **awaiting** for **Phase III** clinical studies
- HBV infection is difficult to be eradicated because of the viral genetic reservoir (cccDNA) and of the integration of HBV-DNA fragments
- The **HBV interaction** with the **hepatocyte** is **pervasive** and **complex** and could make it difficult to identify molecules acting exclusively on the virus machinery
- An **effective** and **specific immune control** is **required** to achieved a **functional cure** of HBV infection

Bruegel il Vecchio, 1559, Proverbi

CPG EASL 2017, Brunetto MR, Asian Pacific Digestive Week 2017, AASLD-HBV SIG 2020

Treatment combination to cure HBV infection and disease

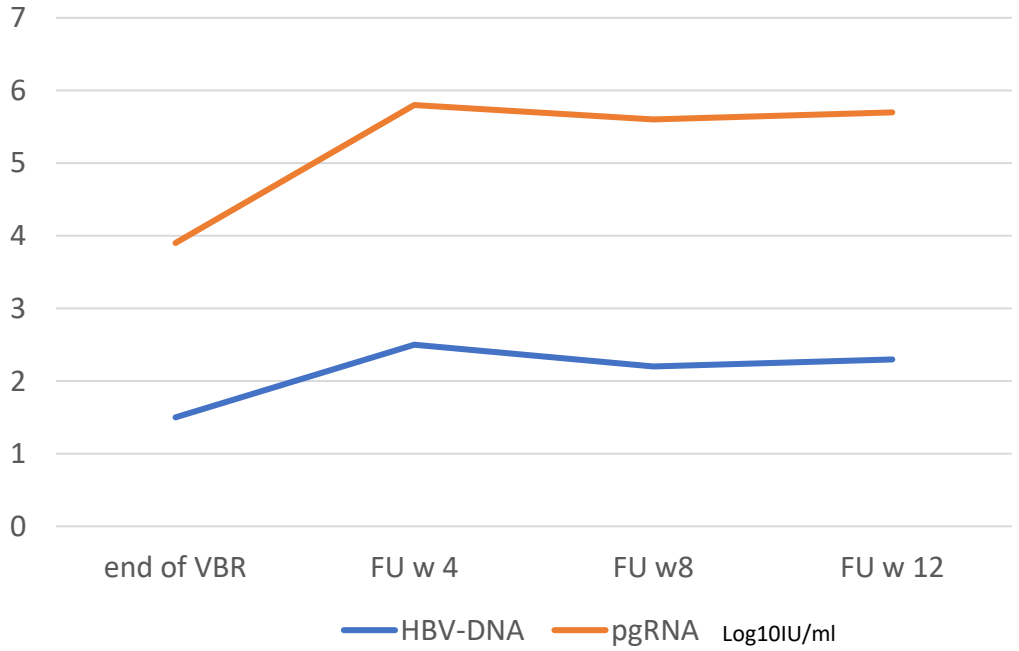


Modified from Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88

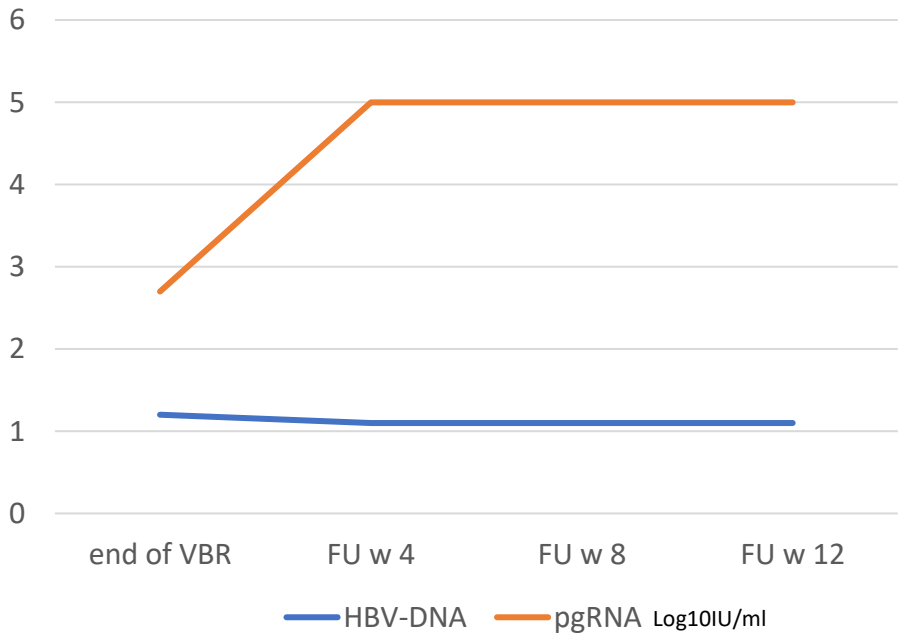
HBV PGRNA and HBV-DNA rebound immediately following discontinuation of the Core Inhibitor VEBICOR despite NA treatment in patients with HBeAg positive CHB infection: findings from a Phase 2 open label study

- ✓ Vebicor (VBR) is a 1° generation **Core inhibitor**, that was administered for 24 weeks in HBeAg positive pts
- ✓ 39 HBeAg positive patients were followed-up for 3 months after VBR discontinuation

21 treatment Naive HBeAg pos patients



18 virologically Suppressed HBeAg pos patients

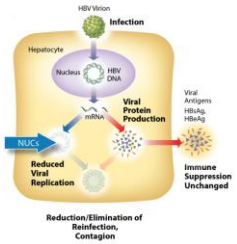


- ➢ The study shows and **additive on-treatment antiviral effect** of VBR when combined with NA
- ➢ The rapid **significant increases** of **HBV pgRNA** and **HBV-DNA** in the setting of continued **NA treatment following VBR discontinuation** provide further evidence of the **important contribution of CAM** to further **deepen viral suppression** in combination therapy

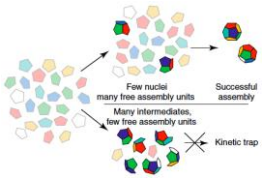
Yuen MF et al , AASLD 2021

Efficacy and Safety of the siRNA JNJ-3989 and/or the Capsid Assembly Modulator JNJ-6379 for the Treatment of Chronic Hepatitis B Virus Infection : Results From the Phase 2b REEF-1 Study

NA

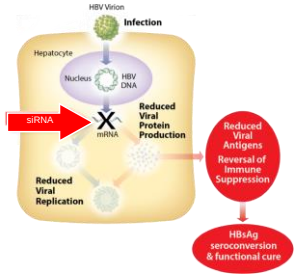


± **CAM**



JNJ-6379 induces the formation of non-infectious viral particles that are devoid of HBV DNA and RNA

± **siRNA**

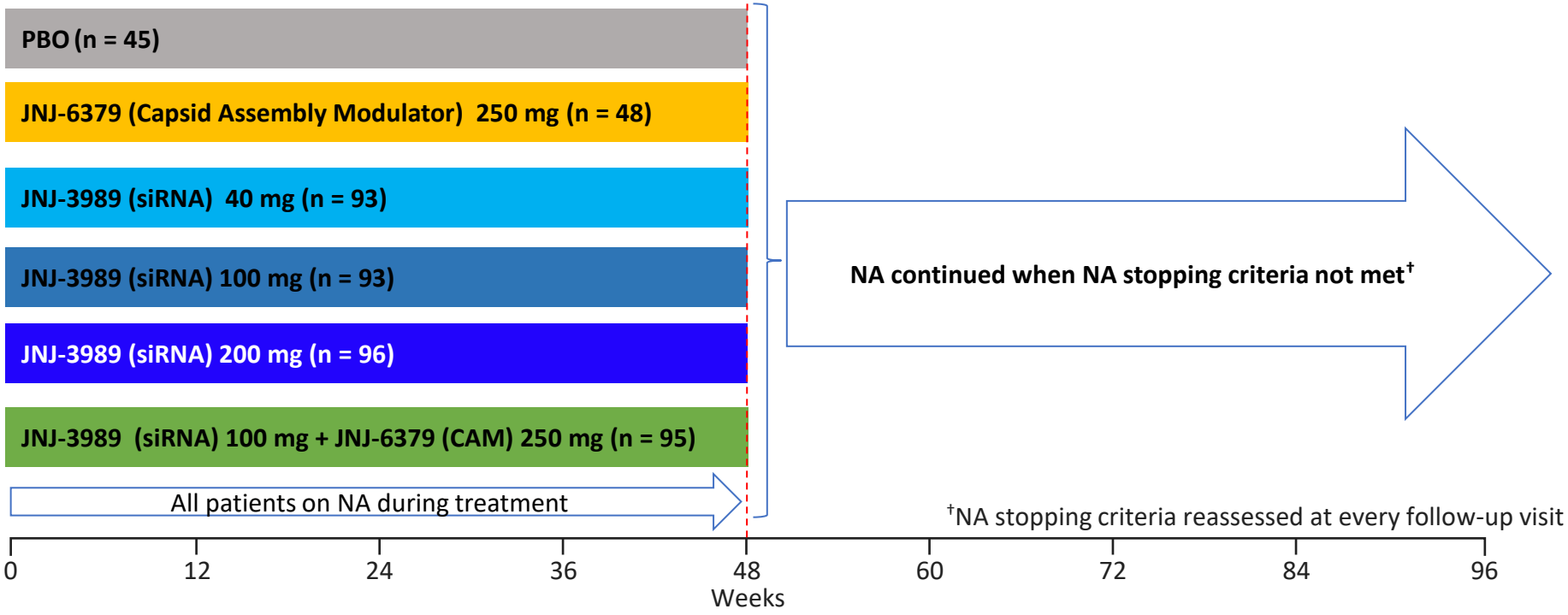


JNJ-3989 targets all HBV RNAs, reducing levels of all viral proteins

Baseline features
- 470 CHB
- 141 (30%) HBeAg pos
- 174 (37%) not currently treated
- 193 (41%) Asian

Inclusion criteria:
- Active CHB (NCT or NA suppressed)
- HBsAg > 100 IU/mL at screening
- Non-cirrhotic (Fibrosis Stage F0-F2)

Stratification:
- HBeAg Status (HBeAg positive vs negative)
- Treatment History (NCT vs VS)

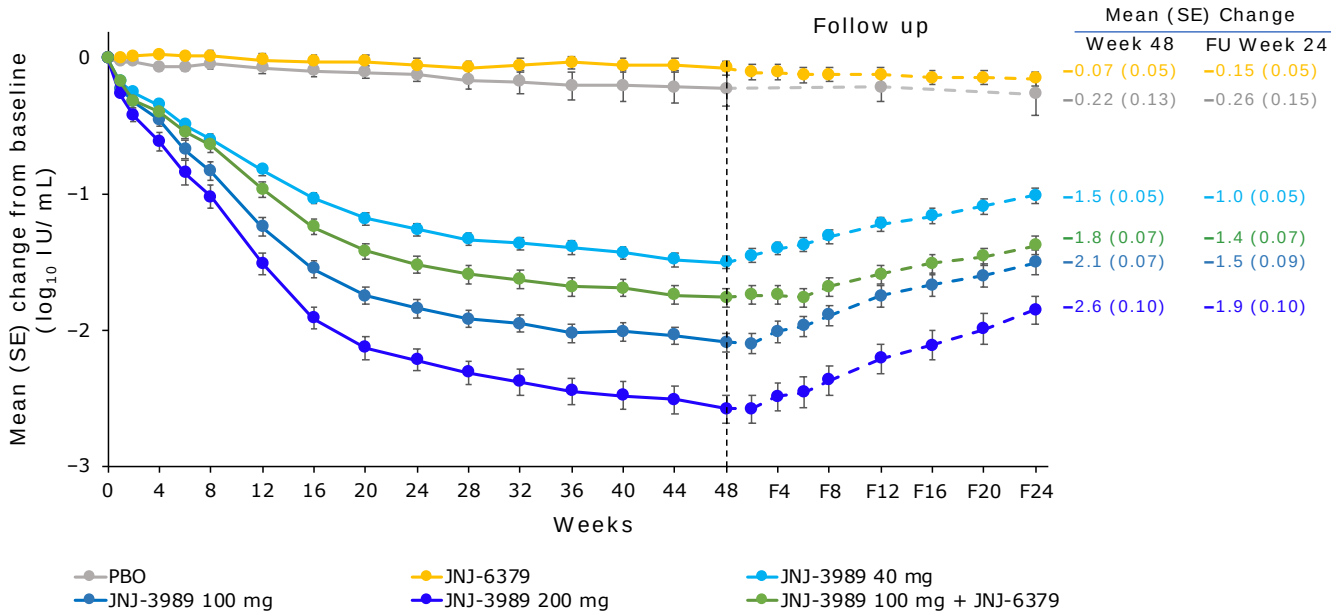


Primary endpoint: Proportion of patients meeting **NA stopping criteria**

ALT <3x ULN,
HBV DNA <LLOQ,
HBeAg negative,
HBsAg <10 IU/mL

Yuen M-H et al, ASSLD 2021

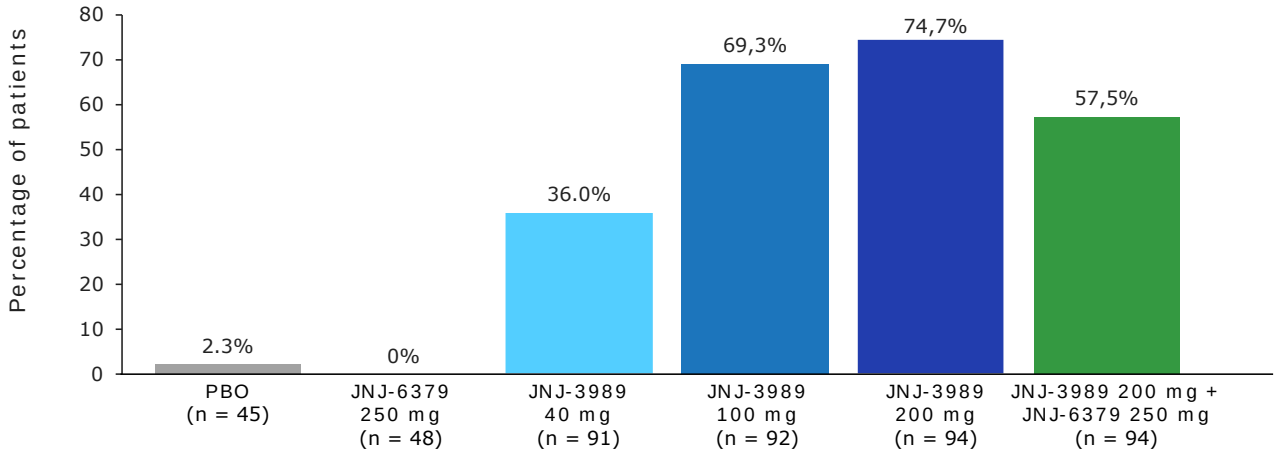
REEF-1: HBsAg Over Time



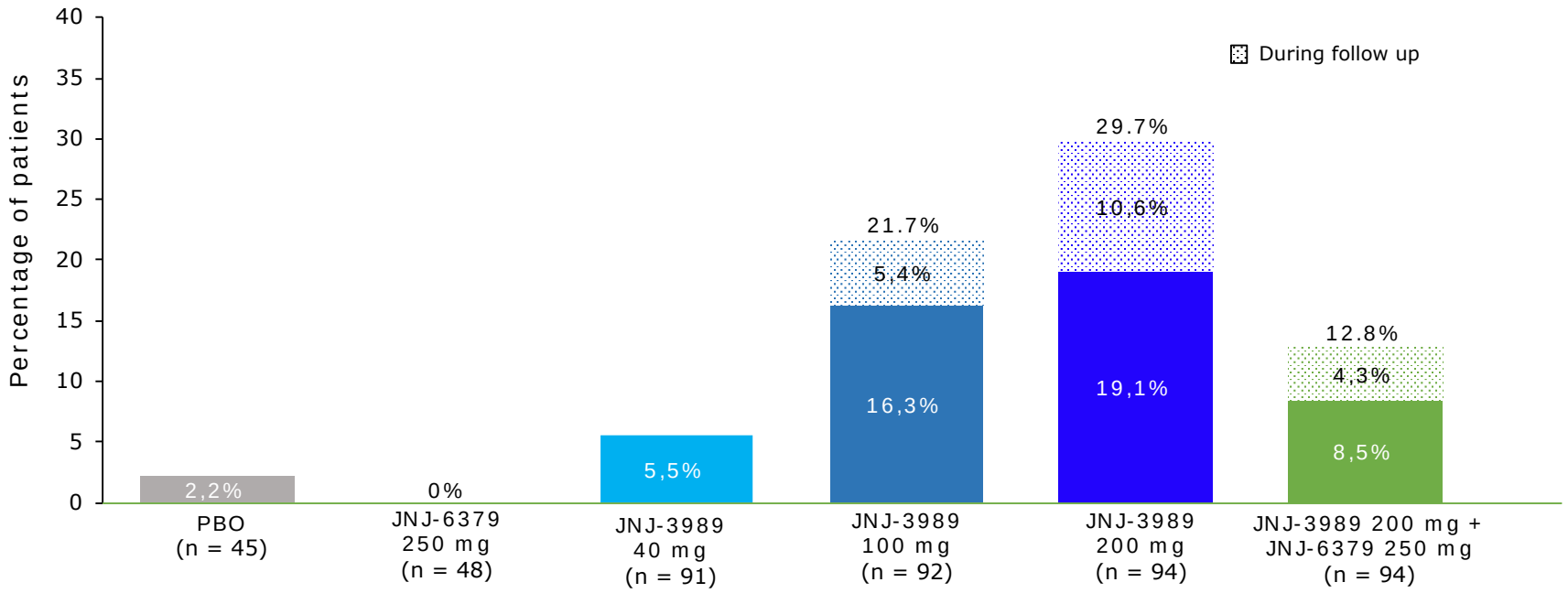
- ✓On treatment **1.5- 2.6 log** HBsAg decline in siRNA treated patients
- ✓**0.4-0.6 log** HBsAg rebound in the 24 week post treatment follow-up

The greatest reduction of HBsAg levels from baseline was seen in the JNJ-3989 200 mg arm (–2.6 log_{10} IU/mL), with 74.7% of patients achieving HBsAg <100 IU/mL

Percentage of Patients Achieving HBsAg <100 IU/mL at Week 48



REEF-1: Percentage of Patients Meeting NA Stopping Criteria*



*ALT <3× ULN, HBV DNA <LLOQ, HBeAg negative, and HBsAg <10 IU/mL.

- The majority of patients meeting NA stopping criteria in the JNJ-3989 arms during and after the 48-week treatment were VS and HBeAg negative

- ✓ A **dose dependent response** was observed, with 19.1% of patients meeting the primary endpoint (NA stopping criteria) in the **JNJ-3989 (siRNA)** 200 mg arm at Week 48
- ✓ The **combination of antivirals** used in this study (JNJ-3989 and/or JNJ-6379 + NA) **is insufficient** to **achieve functional cure** (ie, HBsAg seroclearance) in spite of a 48 week treatment
- ✓ Combination studies of JNJ-3989 with other mechanisms of action are ongoing

Treatment combination to cure HBV infection and disease

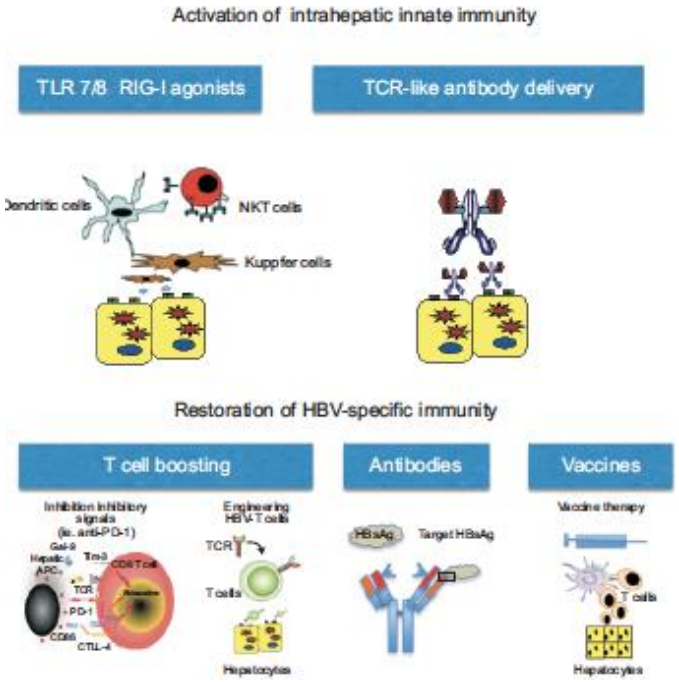
Nucleos(t)ide analogue + **Viral antigen inhibitor** + **Immune modulation** + **cccDNA inhibitor**

To control viral replication and cccDNA re-amplification
(efficacy is function of the antiviral potency)

To inhibit HBV life cycle processes
(entry, mRNA transcription, capsid assembly, viral protein secretion)

To activate or restore HBV targeting immune response

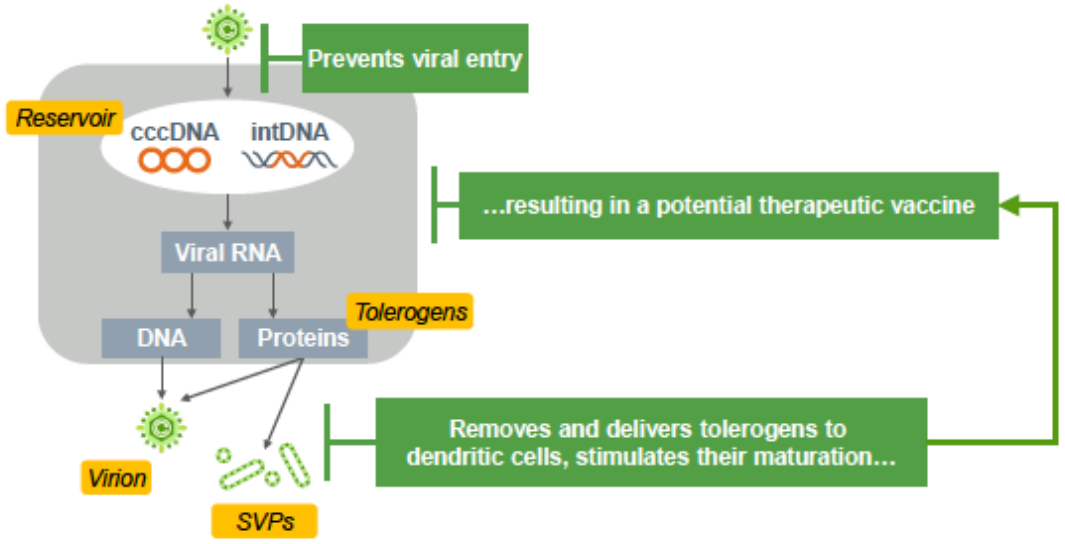
To silence or eliminate cccDNA



Functional cure

Modified from Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88; Bertoletti A et al ; Gut&Liver 2018

VIR 3434: Potentially transformative HBV therapeutic vaccine



VIR-3434 is a **mAb targeting** a conserved region on **HBsAg** that allows it to **neutralize** strains from all 10 HBV genotypes and shows a potential broad, **potent antiviral** spectrum:

- It specifically targets the HBsAg antigenic loop on HBsAg, **preventing viral entry**
- through a process called opsonization, it also helps **remove HBV virions** and **SVPs** from the blood.

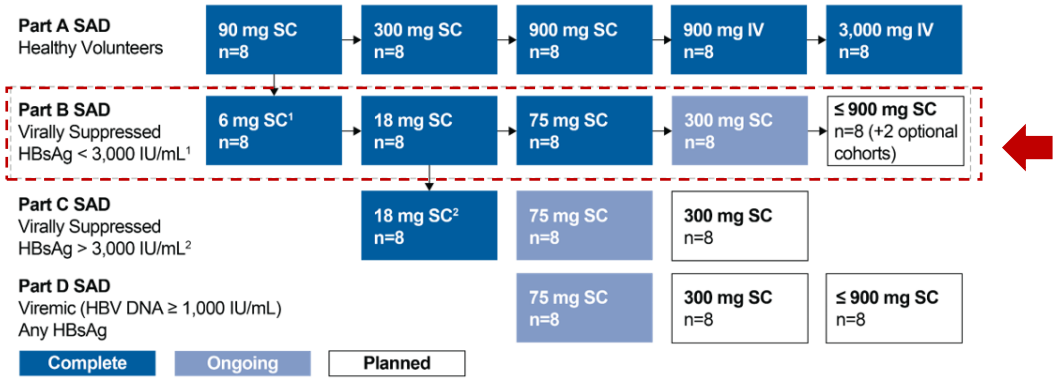
VIR-3434 also has the **potential to activate the immune system**:

- due to specialized mutations in the Fc domain (enhancing binding to the FcR Iia activating receptor), VIR-3434 has the potential to **act as a T cell vaccine**. VIR-3434 is designed to capture virions and SVPs, deliver such virons and SVPs to DCs, and instruct these DCs to mature and stimulate T cells to mature and stimulate T cells that can eliminate HBV infected hepatocytes.
- VIR-3434 has the potential to **act via ADCC** (antibody dependent cellular toxicity): by binding to HBsAg at the cell surface, it recruits NK cells to eliminate infected hepatocytes. The Fc domain of VIR-3434 has been engineered to promote ADCC.
- by **reducing the amount of HBsAg in the blood**, VIR-3434has the potential to remove a brake on the immune system by decreasing the ability of HBV to suppress it.

Rapid HBsAg reduction in NUC-suppressed patients with CHB: preliminary results from a phase 1 study evaluating a single dose of VIR-3434, a novel neutralizing, vaccinal monoclonal antibody

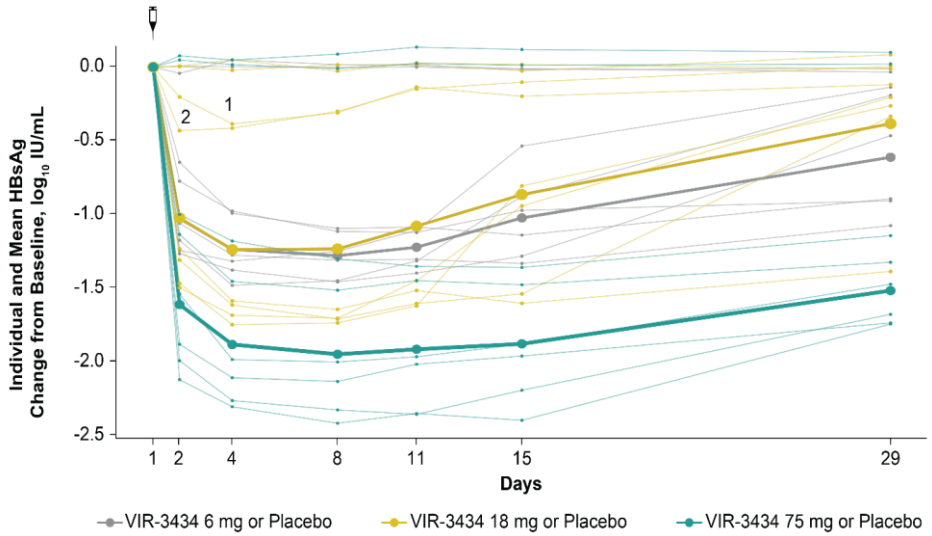
Kosh Agarwal et al, AASLD 2021

Clinical development plan



- In Part B, 8 participants per cohort were randomized in a 6:2 ratio to receive a single dose of VIR-3434 or placebo by SC injection
- Preliminary blinded safety and tolerability results and HBsAg data up to at least 4 weeks post-dose are presented for Part B cohorts evaluating doses of 6 mg, 18 mg, and 75 mg

HBsAg decline (log IU/ml)

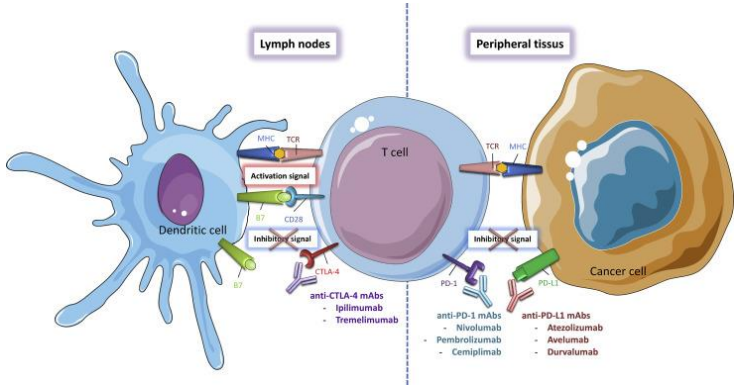


- All the patients had BL HBsAg < 3000 IU/ml (mean 616, range 7.6-2289, IU/ml)
- Most participants rapidly achieved a **> 1 $\log_{10}$ IU/mL** decline in HBsAg within approximately **1 week post-dose**
- **Most** participants achieved **HBsAg < 100 IU/mL** at nadir Excluding those presumed to have received placebo, 5 of 6 participants in the 75 mg cohort (all of whom had a baseline HBsAg > 10 IU/mL) achieved HBsAg < 10 IU/mL at nadir
- Mean HBsAg reductions were **similar** in the **6 mg and 18 mg cohorts**
- Single doses of VIR-3434 were generally well tolerated; all AEs were Grade 1 or 2

Ongoing studies are evaluating VIR-3434

- At higher single doses
- In participants with higher baseline HBsAg values and in those with viremia
- In combination with VIR-2218—an siRNA targeting the HBx region of the HBV genome—in the Phase 2 MARCH study

Checkpoint Inhibitors for the immunotherapy of CHB



- Immune checkpoint inhibitors are monoclonal antibodies (mAbs) directed against negative immunologic regulators that are used to restore the immune response against cancer.
- Approved drugs in oncology setting include anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), **anti-programmed cell death 1 (PD-1)** and **anti-programmed cell death-ligand 1 (PD-L1)**
- **Blockade of PD-1/PD-L1 pathway may lead to a potential cure for HBV.**

PD-L1 antibody ASC22 (ENVAFOLIMAB) in NUC-suppressed pts with CHB
An interim results from a phase IIb clinical trial - a 24-week study

ASC22 (Envafolimab) is a humanized single- domain PD-L1 antibody

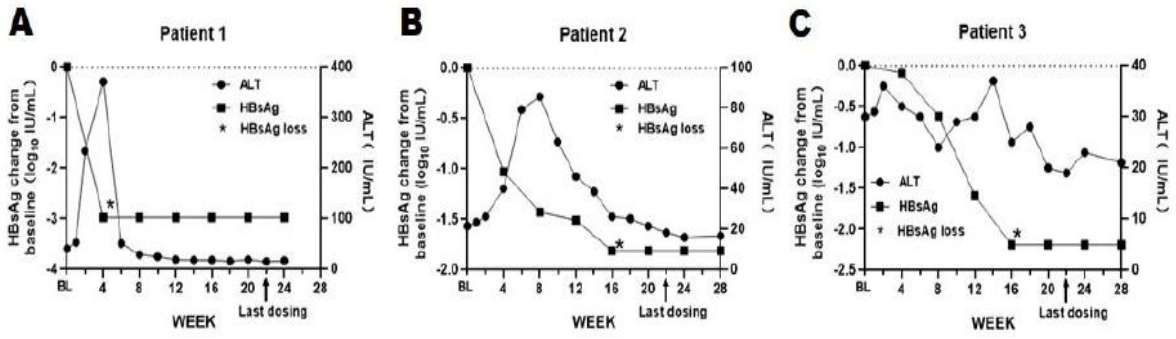
- Randomized, single-blind multi-center Phase IIb trial, **149 CHB patients (negative HBeAg and HBV DNA < 20 IU/ml**) in two cohorts, **24-week treatment** of different dose of ASC22 and 24-week follow-up (NCT04465890).
- In cohort 1, 75 patients were treated with 1 mg/kg ASC22 Q2W (n=60) or placebo (PBO) Q2W (n=15) + NUC.
- The efficacy and safety were assessed in patients who completed 24-week treatment of 1 mg/kg ASC22 (n=33) or PBO (n=11) + NUC

Desnoyer A et al, Eur. J Cancer 2020; Guiqiang Wang et al, AASLD 2021

PD-L1 antibody ASC22 (ENVAFOLIMAB) in NUC-suppressed pts with CHB
An interim results from a phase IIb clinical trial - a 24-week study

- Patients with **BL HBsAg ≤ 500 IU/mL** receiving ASC22+NAs (n=16) had **more significant HBsAg reduction** compared to those receiving PBO+NAs (-0.70 VS 0.00 log10 IU/mL, P < 0.01).
- Among patients with **BL HBsAg ≤ 500 IU/mL**: 7/16 (**44%**) patients in ASC22 group compared to none in PBO group achieved HBsAg **reduction ≥ 0.5 log10 IU/mL** and 3/16 (**19%**) patients **cleared HBsAg**

Add-on ASC22 in NUC-suppressed patients



- HBsAg loss occurred in 3 patients after 4,16 and 16 weeks of treatment and maintained after treatment discontinuation
- In 2 cases HBsAg loss was associated with an ALT flare
- ALT flares were observed also in 4/7 (57%) with HBsAg reduction ≥ 0.5 log10 IU/mL

✓ Subcutaneous administration of ASC22 Q2W for 24 weeks appeared to be safe and well-tolerated,

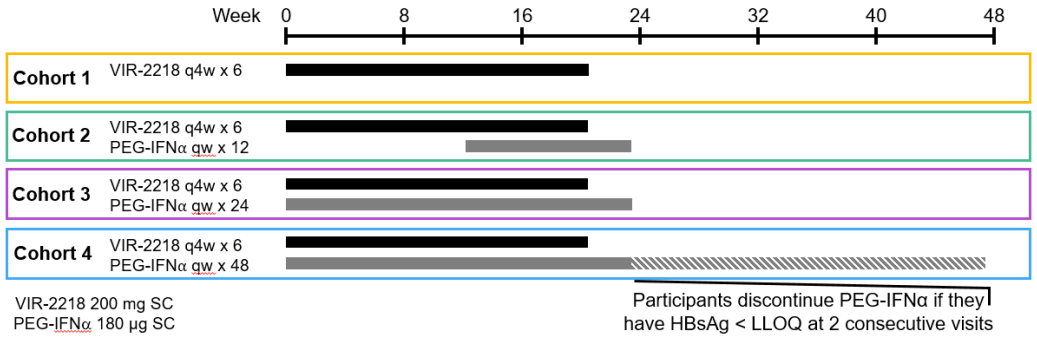
✓ ASC22 can induce HBsAg decline, even HBsAg loss, in CHB patients, especially in those with baseline HBsAg ≤ 500 IU/mL. Further analyses will be performed when all 149 patients complete treatment and follow-up.

Guiqiang Wang et al, AASLD 2021

VIR-2218 (siRNA) alone and in combination with PEG-IFNα in NUC-suppressed CHB patients

Phase 2 study

Study design

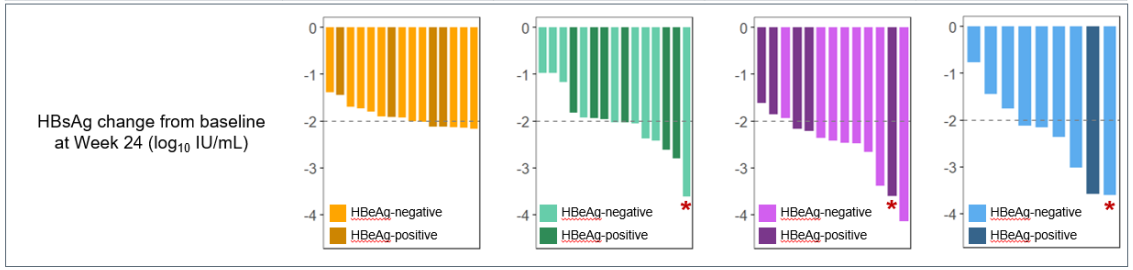


- All participants are virally suppressed
- Preliminary data from Cohorts 1-4 through Week 24 are presented herein

- 26.7-40% HBeAg positive pts
- Most of the patients were Asian (~ 80%)
- 3.2 log 10 IU/ml BL HBsAg serum levels

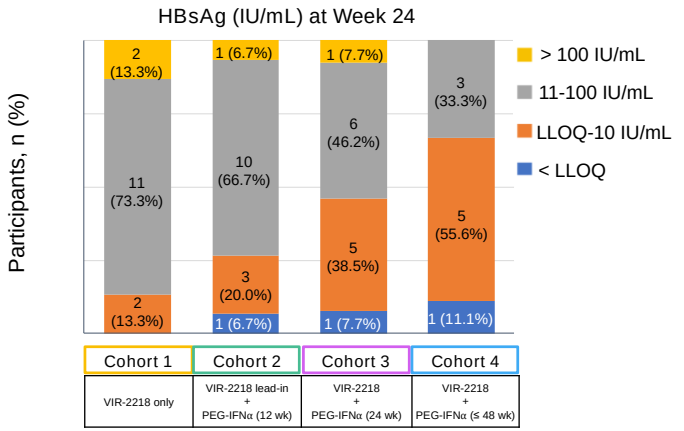
Decline of HBsAg levels

	Cohort 1 VIR-2218 only	Cohort 2 VIR-2218 lead-in + PEG-IFNα (12 wk)	Cohort 3 VIR-2218 + PEG-IFNα (24 wk)	Cohort 4 VIR-2218 + PEG-IFNα (≤ 48 wk)
Week 4, n	15	15	17	13
Mean Change in HBsAg (log_{10} IU/mL)	-0.51	-0.51	-0.92	-1.01
Week 12, n	14	15	16	11
Mean Change in HBsAg (log_{10} IU/mL)	-1.39	-1.42	-1.98	-2.05
At Week 24, n	15	15	13	9
Mean Change in HBsAg (log_{10} IU/mL)	-1.89	-2.03	-2.55	-2.30



*Participant achieved HBsAg < LLOQ (0.05 IU/mL).

HBsAg levels at week 24



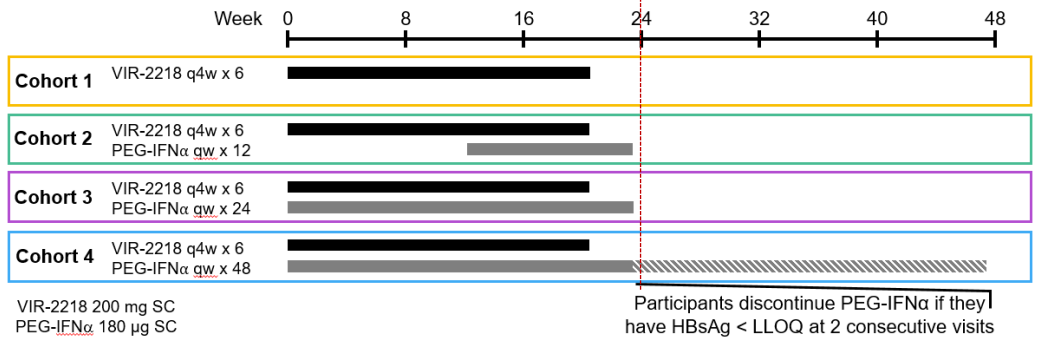
- **92%** of the patients who have completed the Week 24 visit achieved **HBsAg < 100 IU/mL**
- **54.5%** patients receiving **VIR-2218** concurrently initiated **with PEG-IFNα** achieved **HBsAg ≤ 10 IU/mL** at Week 24, compared to those receiving VIR-2218 alone (13.3%)
- Three participants achieved HBsAg < LLOQ by Week 24

Yuen MF, et al, AASLD 2021

VIR-2218 (siRNA) alone and in combination with PEG-IFNα in NUC-suppressed CHB patients

Phase 2 study

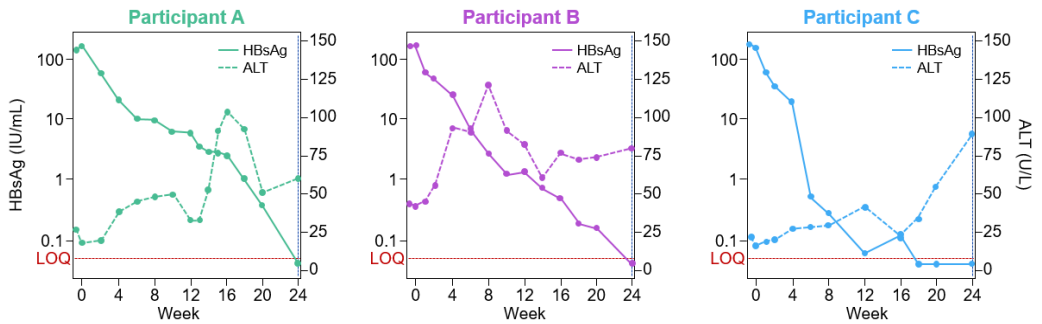
Study design



- All participants are virally suppressed
- Preliminary data from Cohorts 1-4 through Week 24 are presented herein

- 26.7-40% HBeAg positive pts
- Most of the patients were Asian (~ 80%)
- 3.2 log 10 IU/ml BL HBsAg serum levels

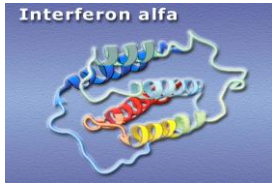
3 patients lost HBsAg



Participant	A	B	C
Cohort	2	3	4
Age (years)	36	56	39
Gender	Male	Male	Male
Baseline HBeAg status	Negative	Positive[1]	Negative
Baseline HBsAg (IU/mL)	134	151	156
Anti-HBs at Week 24	Positive (130.6 mIU/mL)	Negative	Positive (84 mIU/mL)

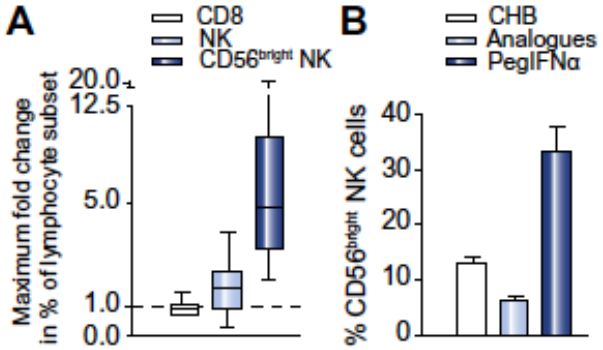
- ✓ Based on the proportion of participants achieving HBsAg < 10 IU/mL at Week 24, PEG-IFNα treatment for > 24 weeks may achieve higher rates of HBsAg loss
- ✓ These data support the hypothesis that the **antiviral activity of VIR-2218** can be **potentiated by concurrent administration of immunomodulators**, such as PEG-IFNα

Yuen MF, et al, AASLD 2021



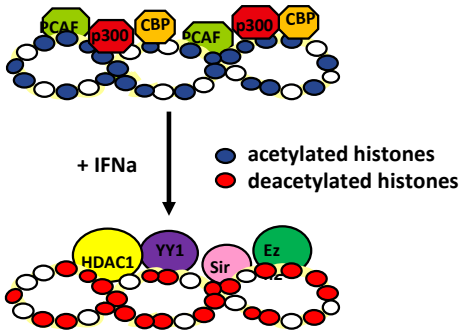
Immunomodulatory Activities

- IFN-α mediates **divergent effects** on the **innate** and **adaptive** arms of the immune system in vivo.
- The efficacy of PegIFNα may be limited by its **depleting effect on CD8 T cells**; conversely, it can cumulatively drive **proliferation**, **activation** and **antiviral potential** of **CD56(bright) NK cells**.



The percentage of CD8 T cells remained stable, whilst NK cells showed a trend to increase. Such boosting of CD56 ^{bright} NK cells was likely to be an immune modulatory effect rather than an indirect effect of viral load reduction

Antiviral Activities



IFNa treatment is accompanied by a decrease in the acetylation of cccDNA bound H4 histones in vitro

Generic

- IFN activates ***multiple genes of the host*** (ISGs), many of which have antiviral activities, interfering viral life cycle.

Specific

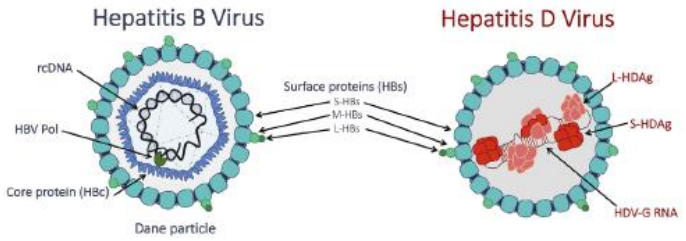
- **IFN-α** inhibits HBV transcription and replication by **targeting the epigenetic regulation** of the nuclear **cccDN**A minichromosome
- **cccDNA degradation** induced by **IFN-α** and **lymphotoxin-β-receptor activation** through up-regulation of APOBEC3A and 3B cytidine-deamin

Micco L, J Hepatol 2013, 58: 225-233; Brunetto M et al, Intervirology 2014; Pollicino T, 2006; Belloni et al., J Clin Invest 2012 ; Lucifora J et al Science 2014

The Alchemist, Bruegel il Giovane 1558

- The preliminary data with the new drugs in development for CHB show different extent of target engagement, inhibition of viral proteins, pgRNA and HBV-DNA production, however we are still awaiting the evidence that functional will be achieved
- A potent and multifaced antiviral activity (i.e. NA + CAM + siRNA) does not appear sufficient to obtain a functional cure
- The combination of antiviral drugs with immunomodulators seems necessary for an effective and persistence control of HBV infection
- A better understading of the mechanisms underlying the spontaneous or therapy induced HBsAg loss is mandatory to design effective combination treatment for CHB

Chronic Hepatitis D



- **HDV** uses the **envelope of HBV** 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**

- **CHD** is considered the **most severe form of viral he**patitis, because HBV/**HDV** infection is **constantly associated** with **liver damage**
- It has been estimated that the **risk of cirrhosis** and **HCC development** in case of **CHD** is **3** and **2 fold increased** as compared to chronic **hepatitis B** and **C**
- Furthermore, the **time to develpment of cirrhosis** in CHD patients is significantly **shorter** as compared to CHB: **5** to **10 years** in **70%** of cases, but **1** to **2 years** in **about 15%** of the patients
- **Virologic** factors (both HDV and HBV), modality of **HDV acquisition**, **phase of HBV infection** at the time of HDV infection and **co-factors** of liver disease **significantly influnce the clinical course of the disease**

Lucifora et al, Antivial Research 2020; Giersch K et al J Hep 2015; Mentha N e al J Adv Res 2019; Farci P et al Sem Liv Dis 2012; Rosina F et al Gastroenterology 1999

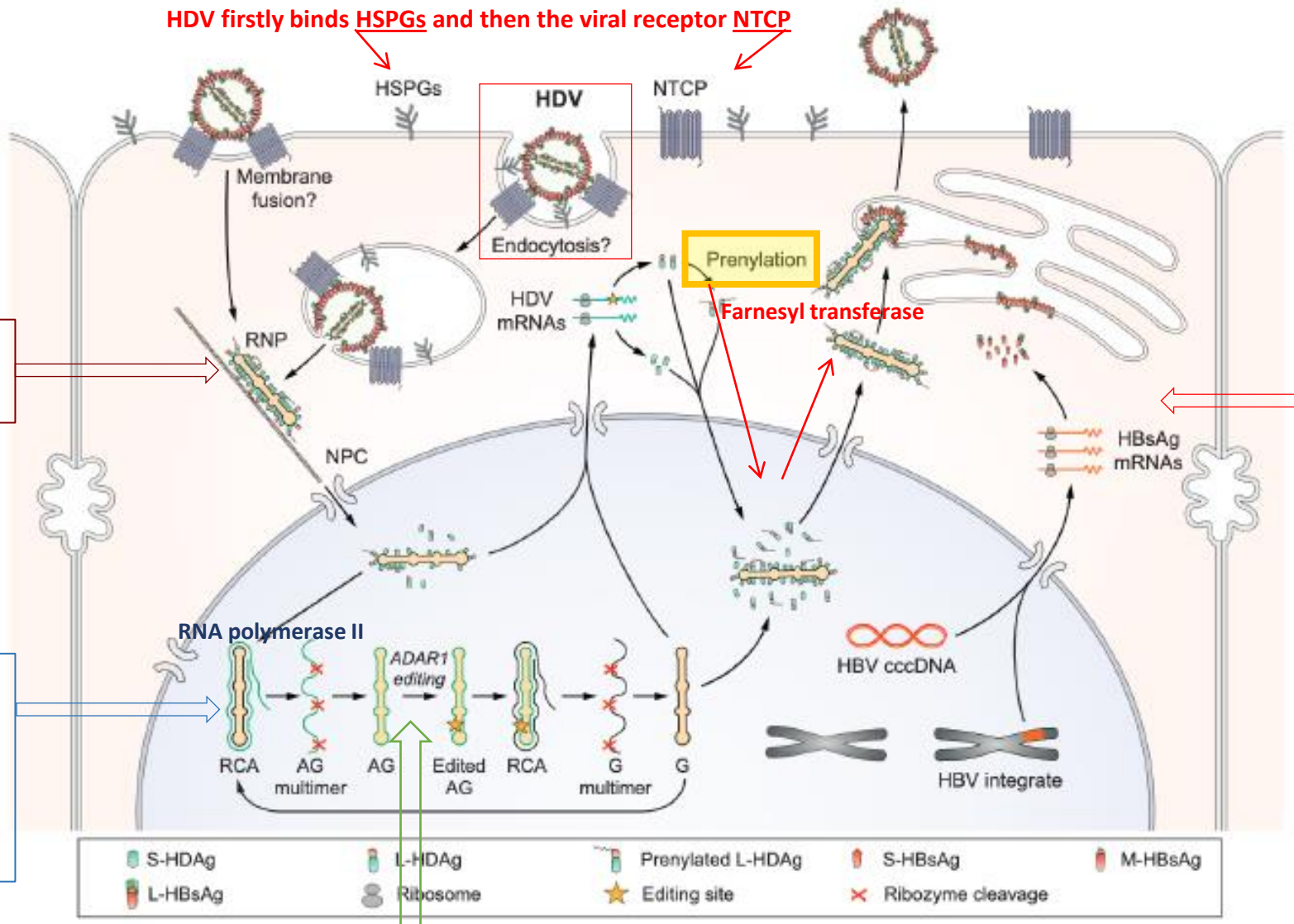
Peg-IFN in monotherapy or with NA in CHD

- On treatment virologic response (**undetectable HDV-RNA**) in **17-48%** of the patients
- At **24 weeks post treatment** discontinuation persistence of virologic response (undetectable HDV-RNA) in **25%** of the patients, with **later relapses** in over **50%** of responders
- A **reduction** of serum **HBsAg** is **mandatory** for the **definitive clearance of the HDV-RNA**
- **HBsAg loss** in about **10%** of the patients → the hallmark of **HDV infection cure**
- **Peg-IFN** combination **with TDF does not** improve the **EOT** HDV response rates
- **Long-term follow-up** [mean time of follow-up was 8.9 (1.6 - 13.4) years] of HIDIT-1 study suggests that **off-treatment HDV RNA response** to PEG-IFNα leads to **improved clinical long-term outcome.**

Heidrich B et al Hepatology 2014; Wedemeyer H et al , Lancet gastro& Hepat 2019; Wranke A et al JVH 2020 Niro GA et al AP&T 2016

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

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

- 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.

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

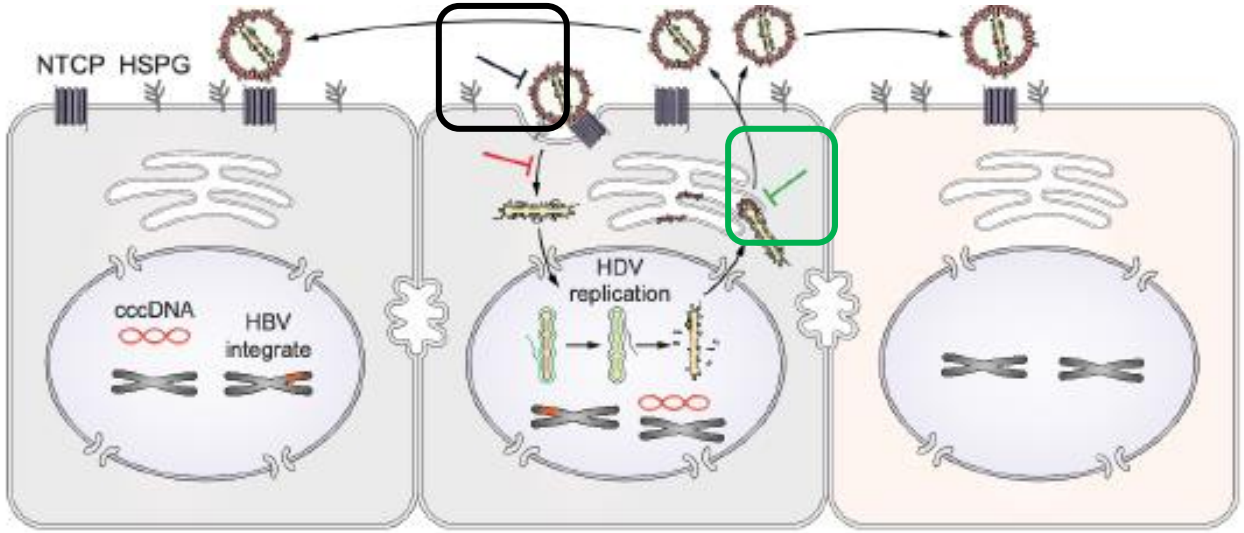
Lucifora et al, Antivial Research 2020; Zhang Z et al J Hep 2021

Old and new targets for HDV infection control and CHD cure

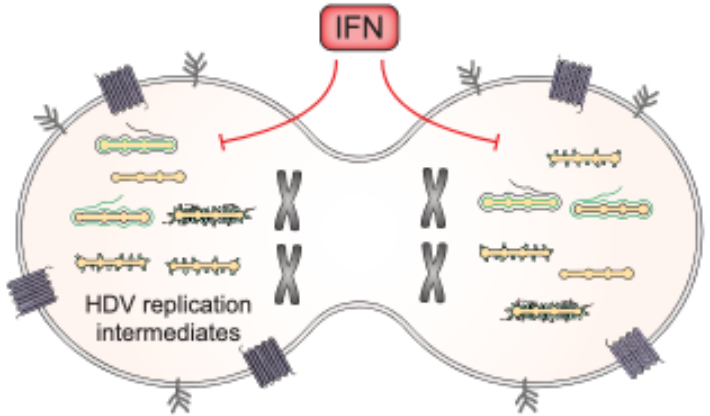
Entry inhibitors

Prenilation inhibitors

IFNs



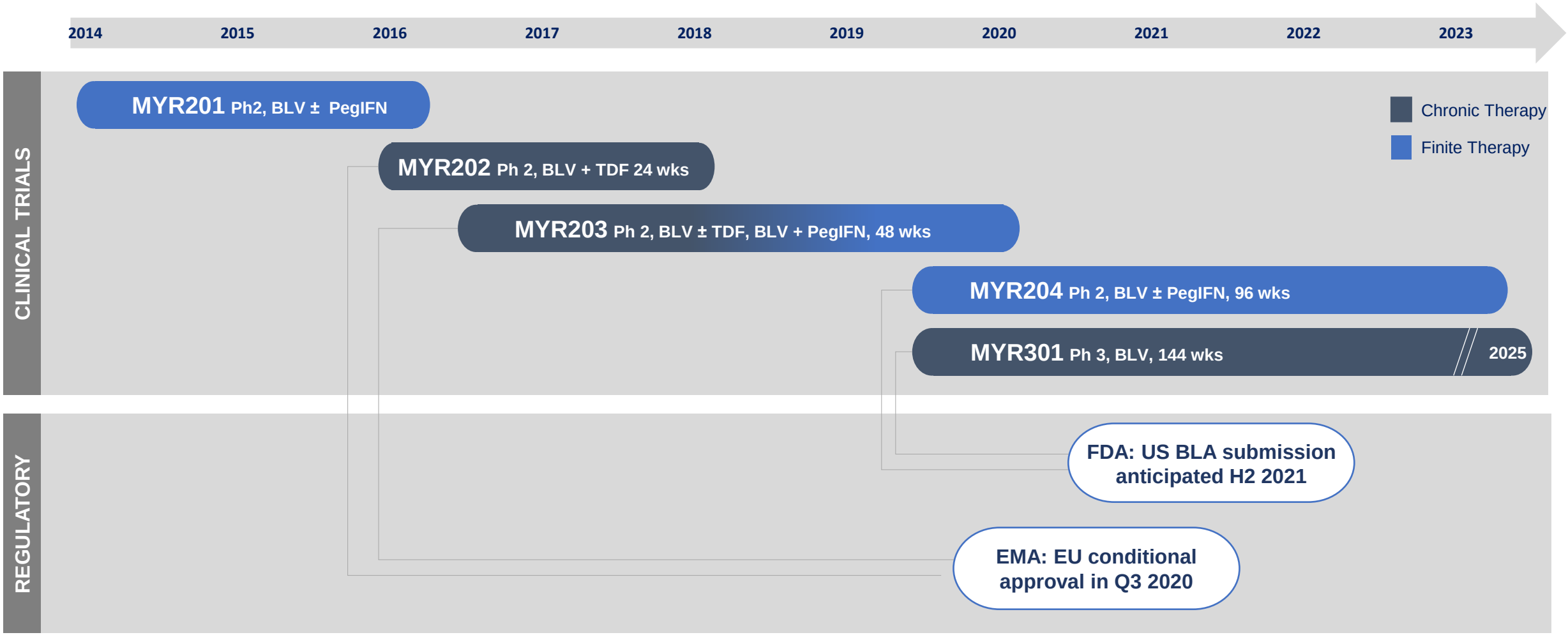
To block *de novo* infection



To block cell division mediated spread

Zhang Z et al J Hep 2021

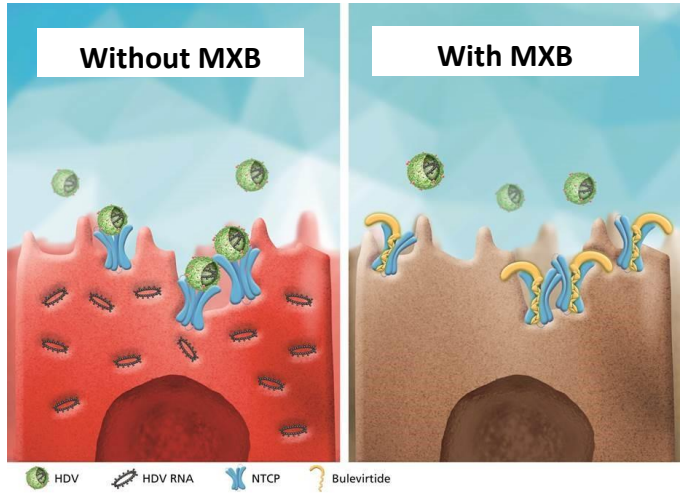
Entry inhibitor - Bulevirtide: Phase 2/3 Clinical Trial Program



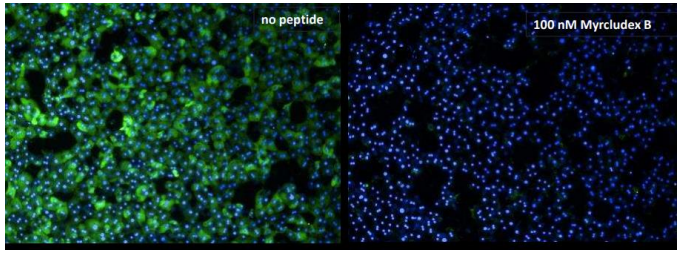
FDA, Food and Drug Administration; PegIFN, pegylated interferon; TDF, tenofovir disoproxil fumarate; US, United States.

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

Myrcludex B (MXB) or Bulevirtide (BLV) is the first-in-class entry inhibitor



with permission of MYR Pharmaceuticals



Immunofluorescence of HBsAg (green) and DAPI (blue) in HBV-infected PHHs at day 15 p.i.

Mode of action:

- MXB 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:

- Self administered s.c injections
- Every day

Approval:

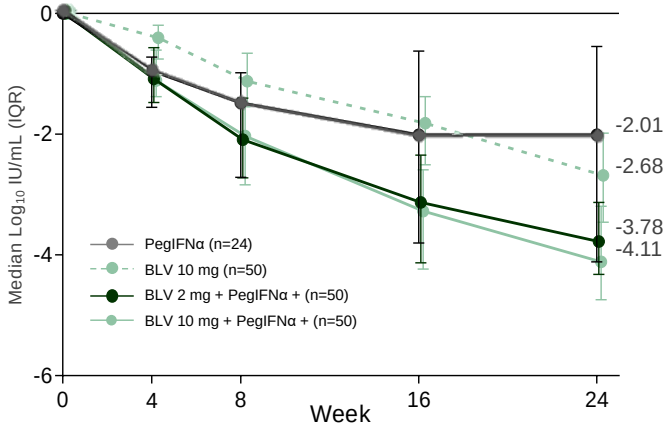
- Conditional approval for 2 mg by EMA (July 20)
- Adults with compensated CHD

Lemp FA and Urban S, 2014

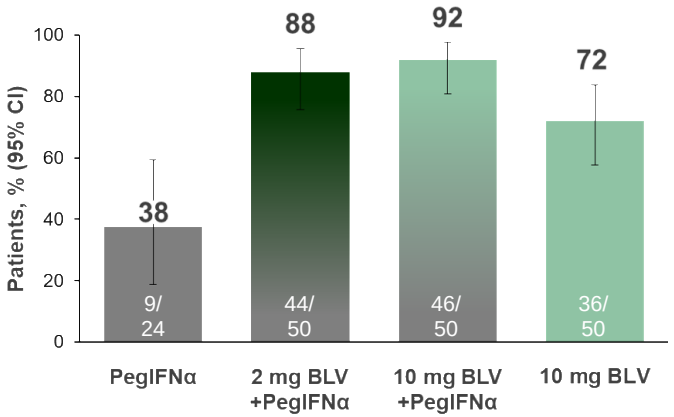
Bulevirtide: Phase 2/3 Clinical Trial Program

- Interim (6 months of treatment) analysis of Phase 2b entry inhibitor ± Peg-IFN (**MYR 204**):
  - **HDV-RNA** decline ≥ 2 log in **72-92%** of pts
  - **ALT** normalization in **24-64%** of pts

HDV RNA Kinetics



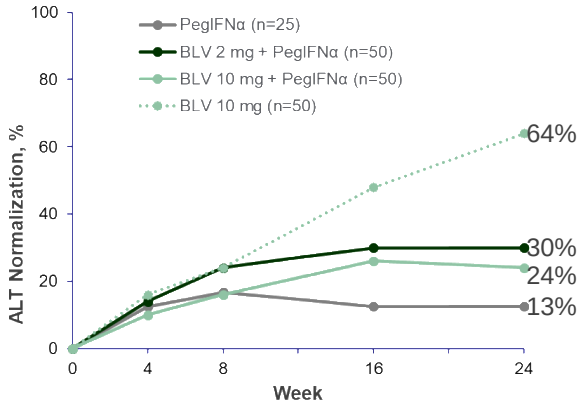
Undetectable HDV RNA or ≥2 log IU/mL decline



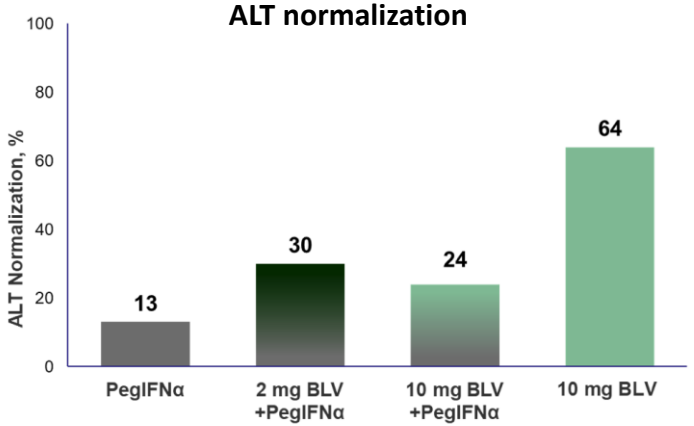
Undetectable HDV-RNA (%)

PegIFN	**13**
BLV 2 + PegIFN	**24**
BLV10+ PegIFN	**34**
BLV10	**4**

ALT kinetics



ALT normalization



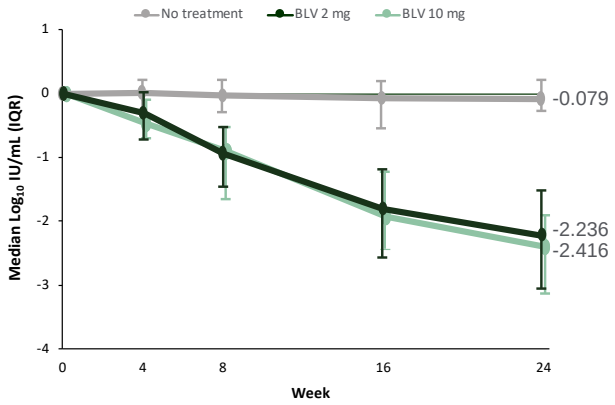
Asselah T, et al. EASL 2021

Bulevirtide: Phase 2/3 Clinical Trial Program

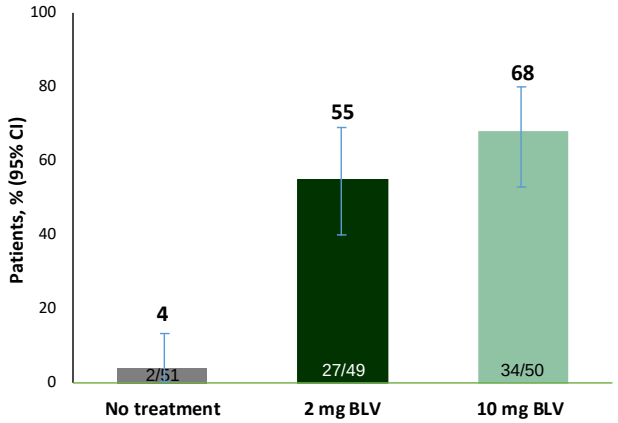
➢ Interim (6 months of treatment) analysis of Phase 2b (**MYR 301**), entry inhibitor (2 or 10mg) monotherapy:

- **HDV-RNA** decline ≥ 2 log in **55-68%** of pts
- **ALT** normalization in **53-38%** of pts

HDV RNA Kinetics



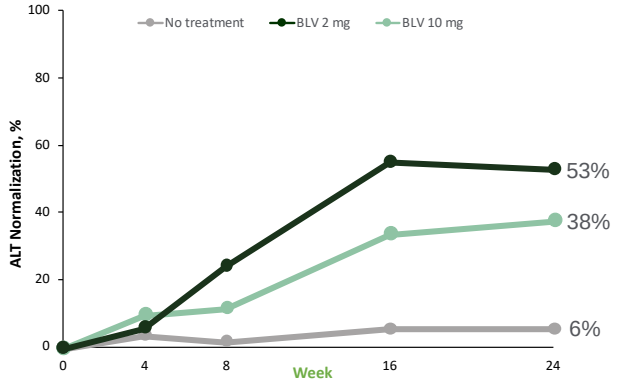
Undetectable HDV RNA or ≥2 log IU/mL decline



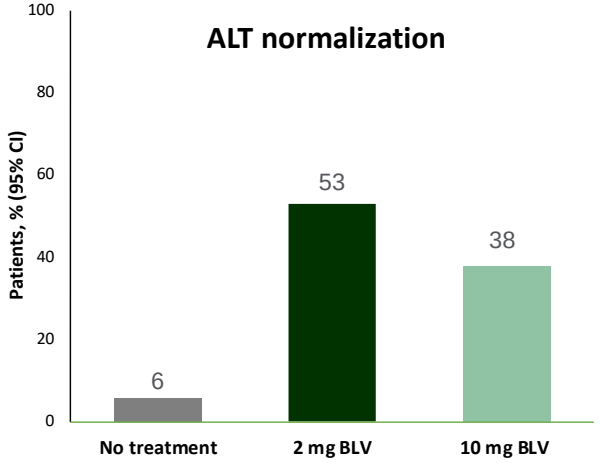
Undetectable HDV-RNA (%)

No treatment	**0**
BLV 2	**6**
BLV 10	**8**

ALT kinetics



ALT normalization

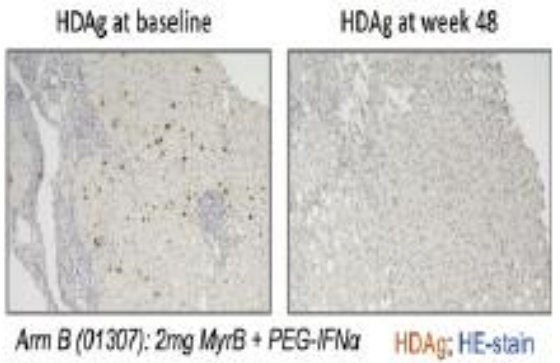


Rapid ALT reduction and normalization were observed in >50% of patients in the entry inhibitor 2-mg arm after 24 weeks of treatment

Wedemeyer H, et al. EASL 2021.

Buleviritide: Phase 2/3 Clinical Trial Program

- Interim (6 months of treatment) analysis of Phase 2b entry inhibitor ± Peg-IFN (**MYR 204**):
  - **HDV-RNA** decline ≥ 2 log in **72-92%** of pts
  - **ALT** normalization in **24-64%** of pts
- Interim (6 months of treatment) analysis of Phase 2b (**MYR 301**), entry inhibitor (2 or 10mg) monotherapy:
  - **HDV-RNA** decline ≥ 2 log in **55-68%** of pts
  - **ALT** normalization in **53-38%** of pts
  - Rapid ALT reduction and normalization were observed in >50% of patients in the entry inhibitor 2-mg arm after 24 weeks of treatment
- **Plasma HDV-RNA decline** correlates with **intrahepatic decrease of HDV-RNA** and **HDAg** in **MYR 203** study
- Entry Inhibitor treatment was also associated with **reduced expression** of **interferon-stimulated genes** and **inflammatory chemokines** and cytokines **in MYR 203** study
- **HBsAg response** (≥ 1 log decline) 24 week after EOT in **13 to 40%** of patients receiving entry inhibitor + Peg-IFN in **MYR203**

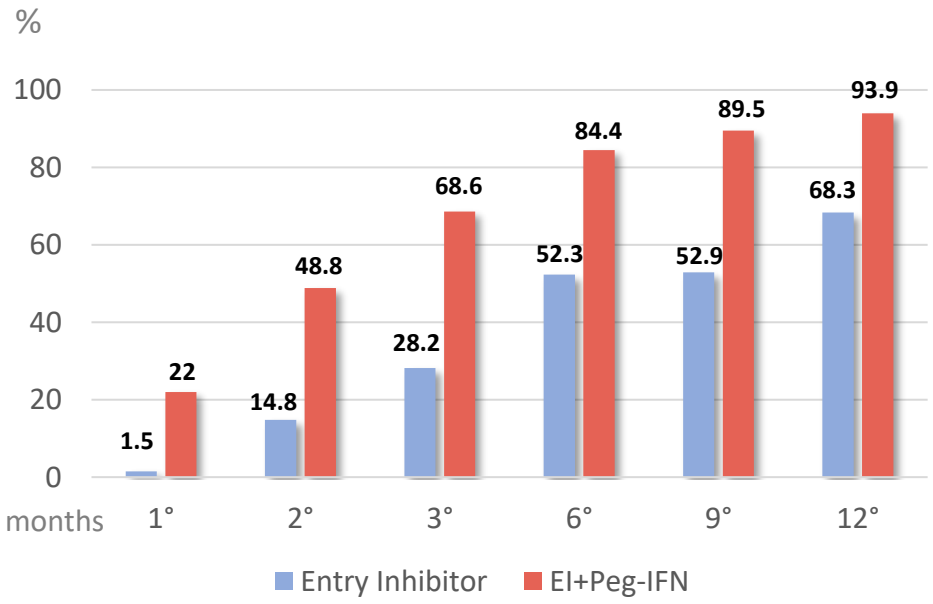


Asselah T, et al. EASL 2021; Wedemeyer H, et al. AASLD 2018; Allweiss. AASLD 2021;Wedemeyer H, et al. EASL 2020 Wedemeyer H, et al. EASL 2021.

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

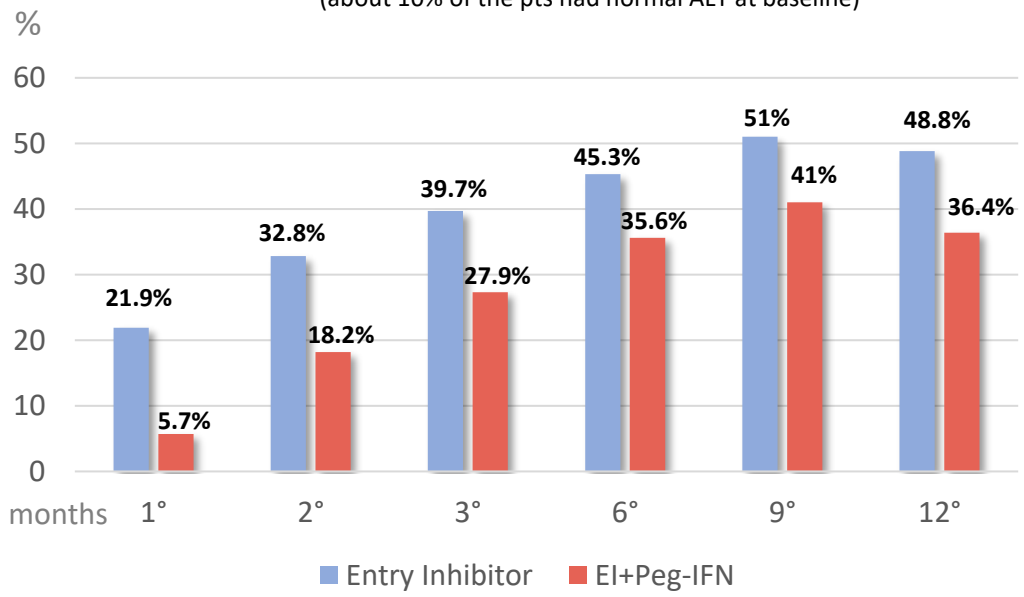
- 145 adults with compensated cirrhosis or severe liver fibrosis (F3) or with F2 fibrosis with persistent ALT >2 x ULN for ≥6 mo (N = 145) were enrolled in a multicenter, observational study;
- 77 received entry inhibitor (2 mg) monotherapy and 68 entry inhibitor (2 mg) + Peg-IFN

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.

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

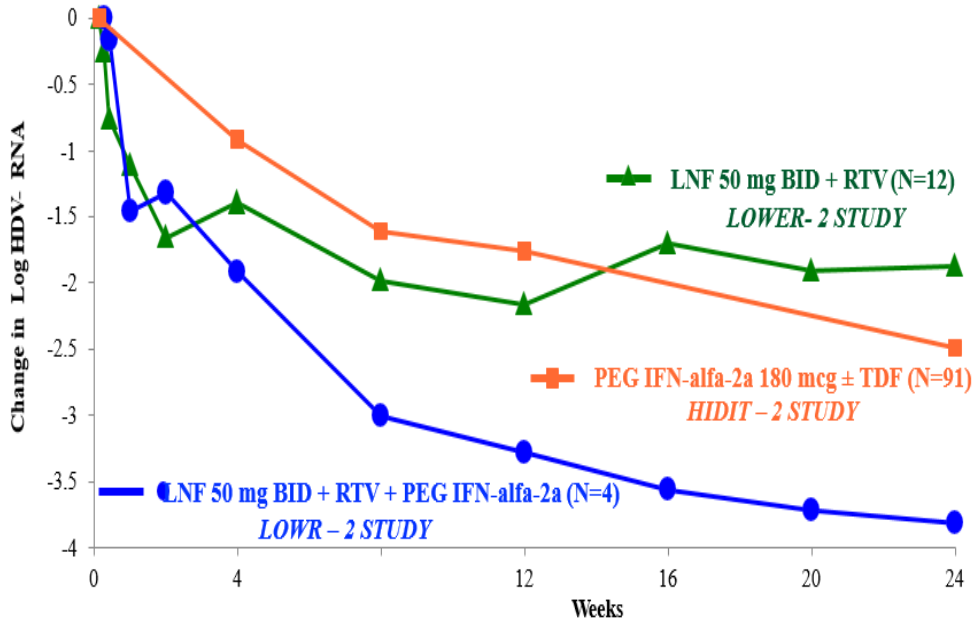
Over 120 HDV patients have been treated in Phase 2 clinical studies evaluating the tolerability and efficacy of LNF, alone and in combinations with other agents, currently a Phase 3 clinical study is planned to enroll 400 pts.

Dose dependent HDV-RNA decline were observed in proof of concept studies: 2 log for 300 mg, 1.54 log for 200 mg and 0.73 for 100 mg at w 4 → but major GI side effects for higher doses

Addition of **Ritonavir** –an inhibitor of CYP3A4, the predominant mediator of Lonafarnib metabolism – achieves greater serum concentrations with less drug to the GI tract (LOWR-HDV studies 1 -4 --LOnafarnib With and without Ritonavir in HDV--)

Elazar M et al in *Hepatitis D, by Rizzetto M 2019*

Lonafarnib + RTV with or without PEG IFNalpha for HDV

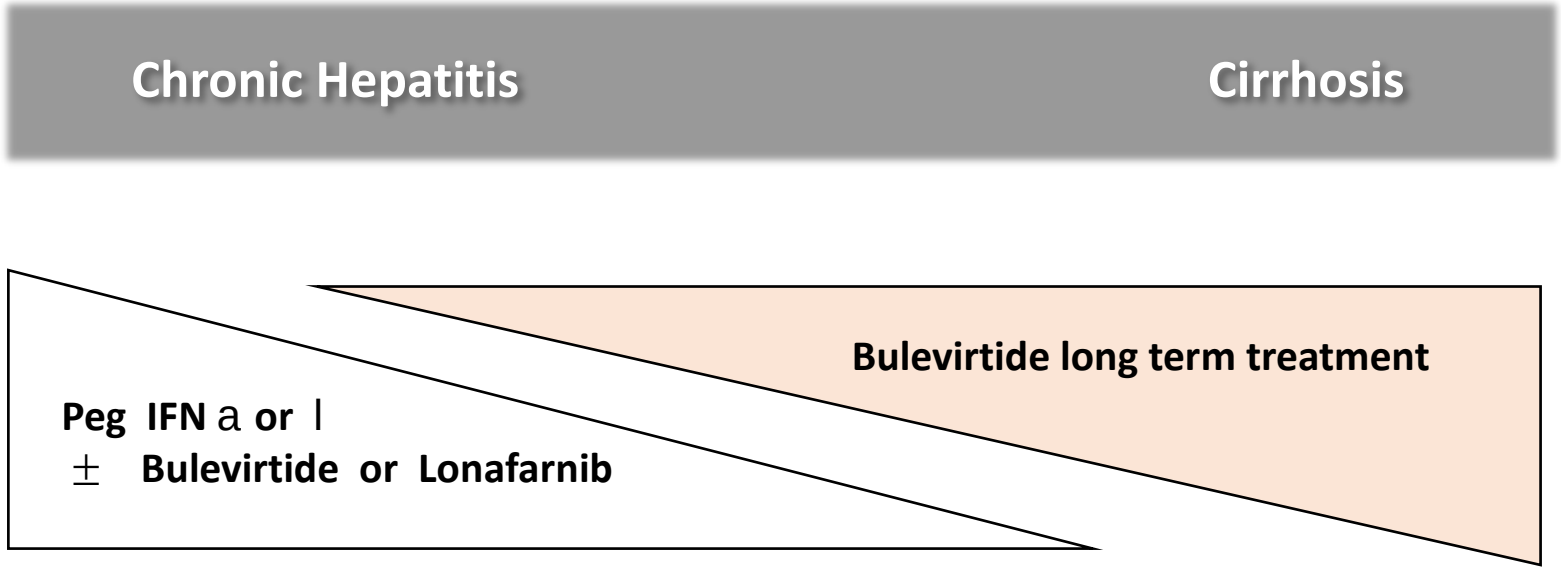


- **All-oral:** Lonafarnib boosted with Ritonavir
  - 39% (7 of 18) patients ≥ 2 log decline or BLQ at Week 24
  - 60% patients normalized ALT at Week 24
- **Combination:** Lonafarnib boosted RTV+PEG IFN-alfa2a
  - 89% (8 of 9) patients ≥ 2 log decline or BLQ at Week 24
  - 78% patients normalized ALT at Week 24
- **Safety:** Predominant AEs for LNF were GI-related (mild/mod.)

- Combination of **LNF+Peg-IFN** achieves the **greatest antiviral responses**
- The **antiviral response** is observed **early,** during treatment, therefore **repeated short** (3 months) courses could be also attempted
- A sub analysis of the study suggests that **LNF 50 mg + RTV 100 mg BID** appeared to be a particularly effective option for patients with **low baseline viral load**, with a **100%** (7/7) response.
- LNF+RTV treatment can result in post-treatment flares, evenutally resulting in viral RNA negativity and ALT normalization in selected patients

Yurdaydin et al, J Hepatol 2018, Abstract #PS-161

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