Le opzioni terapeutiche future per HBV e HDV

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Disclosures

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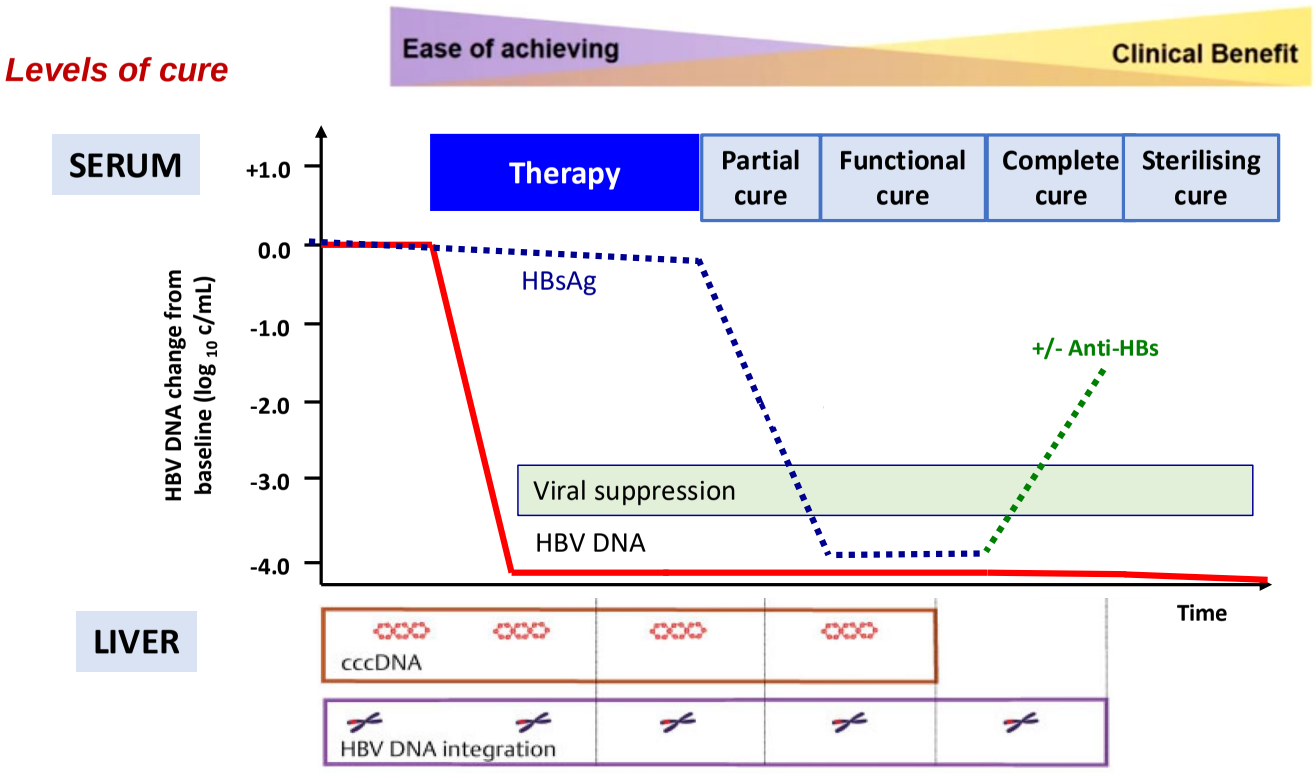
ABBVIE, GILEAD SCIENCES

The changing treatment paradigm in HBV

	Current	Future
Goal	Viral suppression	Cure
Primary endpoint	Serum HBV DNA not detected	Serum HBsAg loss
Serum bomarkers	HBV DNA	qHBsAg, HBV RNA, HBcrAg
Regimen - Type - Drugs - Mechanism of action - Duration	Monotherapy NUCs NRTI Long-life	Combination Multiple DAAs, multiple IM Multiple targets Finite
Population	CHB	CHB, Chronic infection

Future HBV therapies: from «control» to «cure»

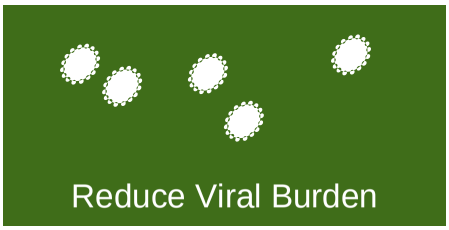


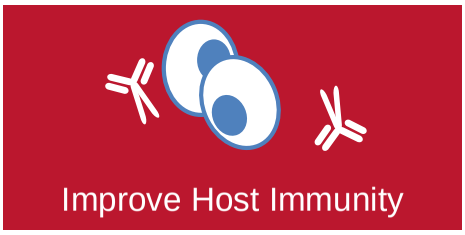
Testoni B et al Semin Liver Dis 2017; 37:231-242

Evolving HBV Therapy: next step «functional cure»

Two strategies

- **Targeting the virus**
- **Targeting host immune response**



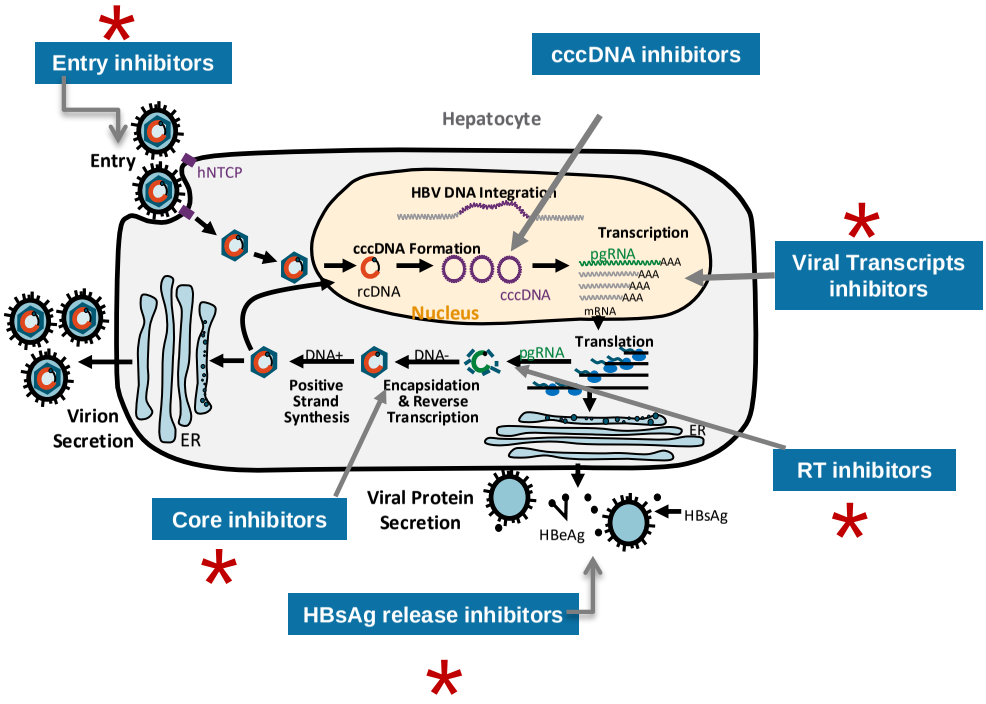


Direct-acting antivirals **Immune therapies**

Combinations of novel therapies

Viral targets & drug discovery to cure HBV infection

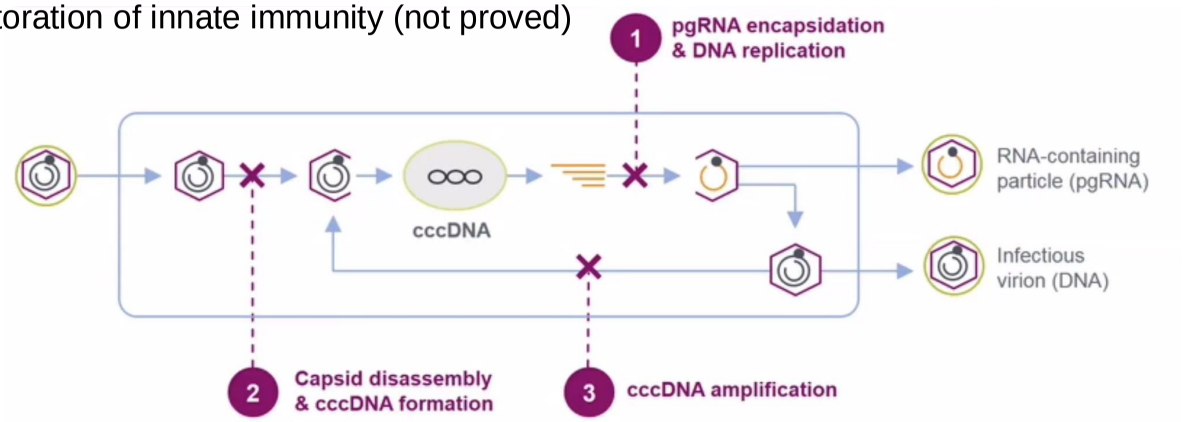
- **Target cccDNA** formation, silencing, destabilization
- **Replication inhibition**
  (pre and post cccDNA targets)
  - Entry
  - Viral transcripts
  - Core
  - RT pol
- **Antigen reduction**
  - HBsAg release
  - Viral transcripts



* = drugs in clinical trials

Core inhibitors (CpAMs, CAMs*)

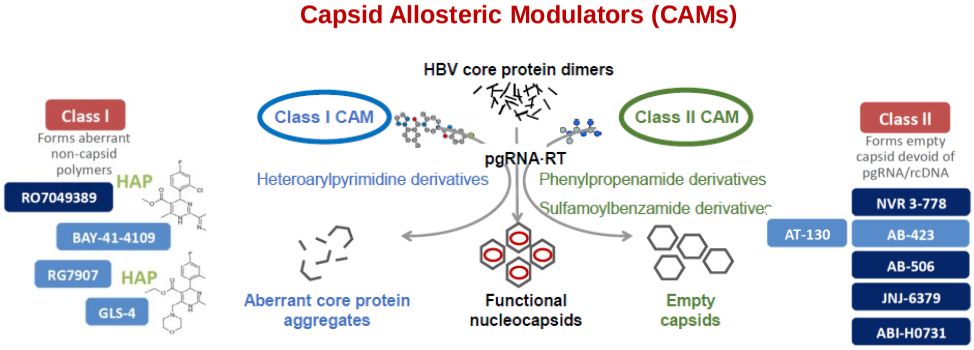
- **Molecular target:** core protein assembly and pgRNA packaging
- **MoAs:**
  - Inhibition of viral replication by blocking the formation of viable RNA nucleocapsids
  - Target cccDNA replenishment (mature capsid recycling)
  - Prevention of cccDNA formation in newly infected hepatoytes
  - Target the interaction between core protein and cccDNA; reduce cccDNA transcription (to be confermed)
  - Restoration of innate immunity (not proved)



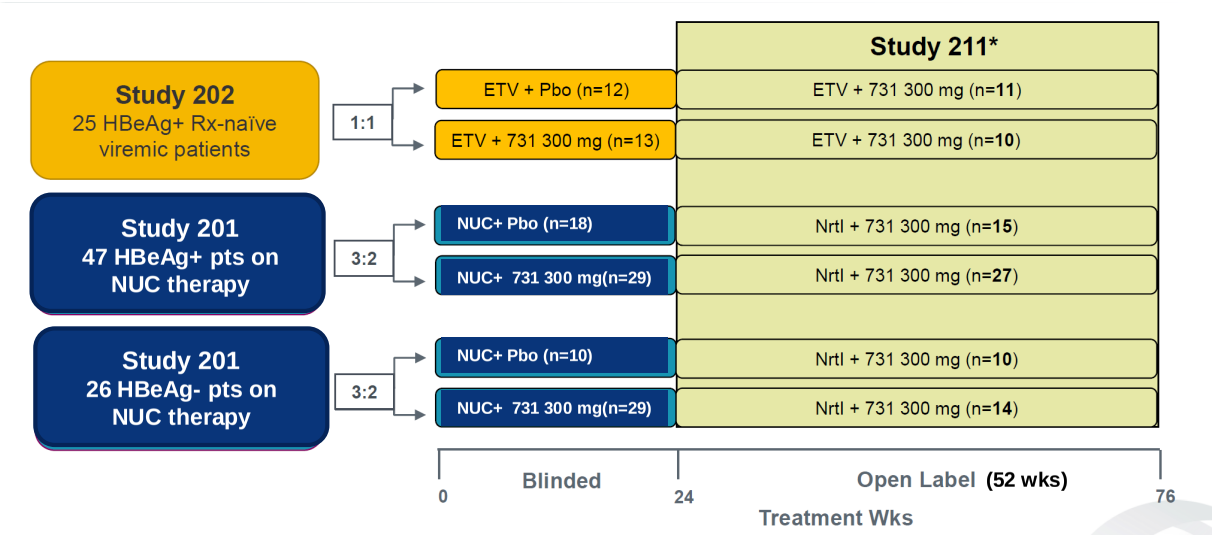
* CpAMs = Core protein Allosteric Modulators, CAMs = Core Allosteric Modulators

Core inhibitors (CpAMs, CAMs)

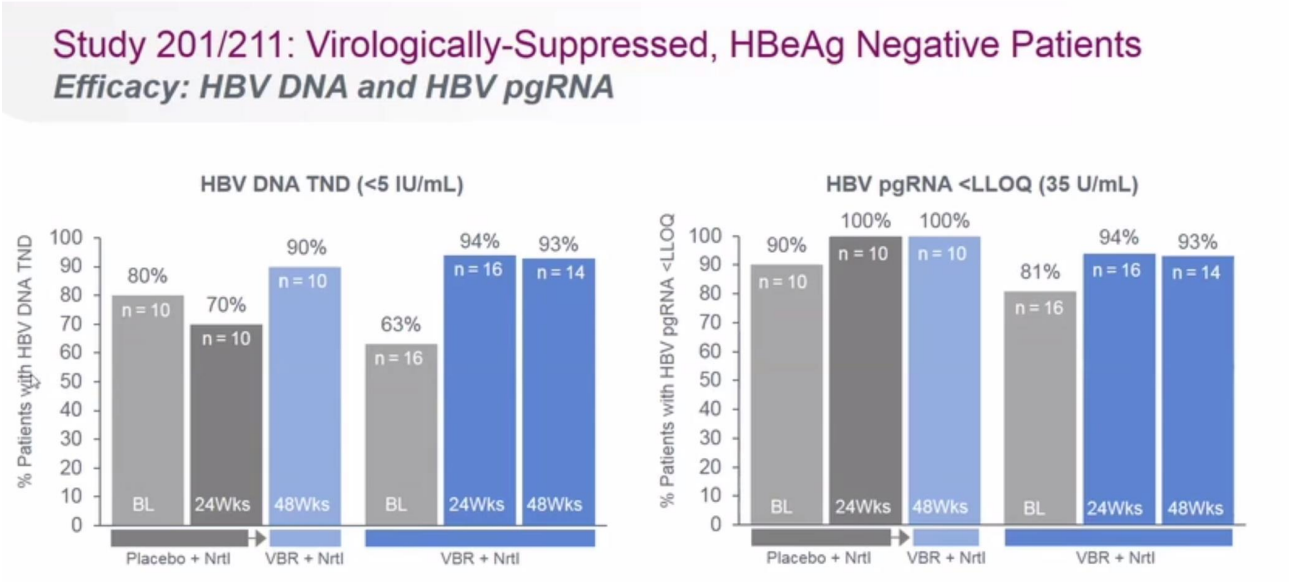
- Several compounds under development and clinical evaluation
- Easy to use (once daily oral regimen)
- Decline in HBV DNA and HBV RNA (target engagement)
- No significant impact on HBsAg or HBeAg decline (so far)
- Risk for initial non-response and resistance
- Side effects: rash (self-limited) and ALT flares



Core inhibitors
ABI-H0731 + NUC (phase 2 clinical studies)



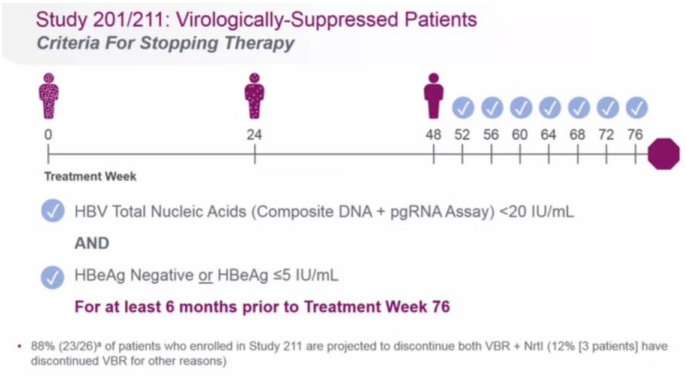
Extended treatment with ABI-H0731+NUC Study 201/211



- 24 weeks of treatment with ABI-H0731 + NRTI resulted in a higher proportion of HBeAg- patients achieving HBV DNA TND by highly sensitive assays compared with placebo + NRTI
- ABI-H0731 demonstrated a favourable safety and tolerability profile
- Data suggest the contribution of ABI-H0731 to the standard of care in achieving more profound viral suppression

S Fung et al EASL 2020

Extended treatment with ABI-H0731+NUC
Study 201-211



S Fung et al EASL 2020

Study 211 Interim Off-Treatment Virologic Results

Number of patients	Discontinued treatment with VBR+Nrtl	Relapsed at post-treatment Week 4	Relapsed at post-treatment Week 8	Relapsed at post-treatment Week 12	Relapsed at post-treatment Week 16	Have not relapsed*
HBeAg negative	23	16	0	3	3	1 4%
HBeAg positive	18	17	0	0	0	1 6%

*These 2 patients have completed the post-treatment Week 8 visit

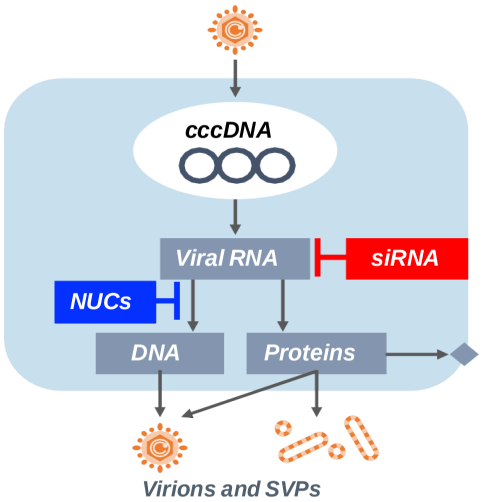
Assembly Bioscences update, November 5, 2020

Next steps:

- Phase 3 registrational program on chronic suppressive therapy in China
- Phase 1, 2 trials of second and third core inhibitor candidates (ABI-H2158,ABI-H3733)
- Phase 2 trial VBR + NUC +RNAi

Viral transcripts inhibitors
RNA interference/Gene silencing

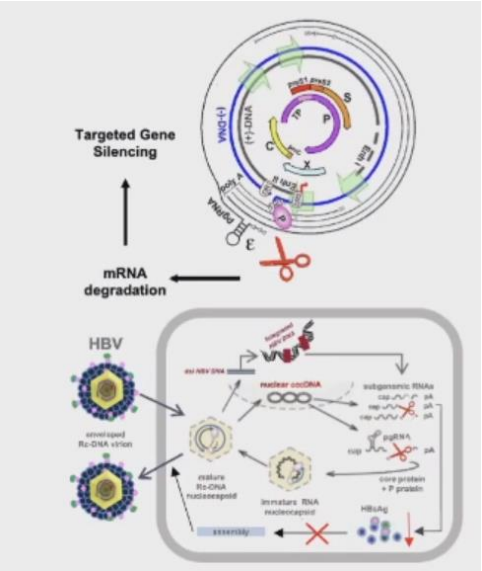
- **Molecular target: viral RNAs**
- **MoAs:**
  - Target the HBV pgRNA replicative intermediate
  - Target all subgenomic RNAs derived from both integrated HBV and cccDNA (reduce all viral proteins)
  - Indirect immune modulation by reducing HBsAg/HBeAg



Viral transcripts inhibitors

RNA interference/Gene silencing

- Multiple platform for delivery; needs to be given IV or SC; risk of allergic reactions
- qHBsAg decline and HBV RNA reduction (target engagement)
- Robust decline of HBsAg in all patients
- Currently given in combination with NA, or CpAMs + NA



siRNAs
- JNJ-3989
- VIR-2218

ASO/LNAs*
- RO7062931
- GSK 3389404
- ISIS 505358

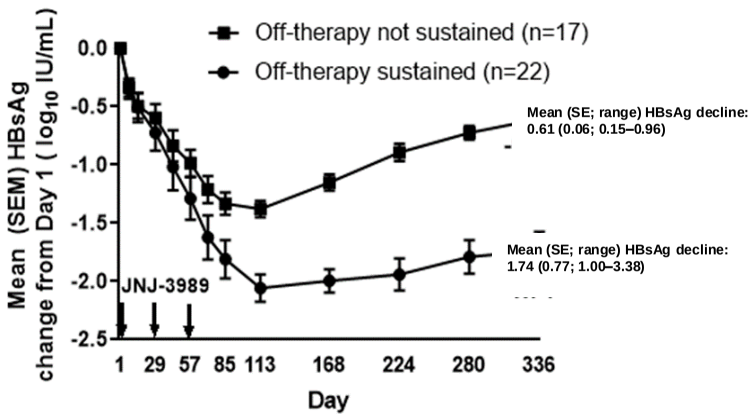
* Anti-sense Oligonucleotide (DNA) with locked nucleic acid (LNA) that resuts in RNAseH mediated degradation of HBV transcripts

Translation inhibitors in NA suppressed pts

JNJ-3989 (ARO-HBV Phase 2 study)

- 40 HBeAg+ or HBeAg- patients treated with ≥100 mg JNJ-3989 sc on Days 1, 27 and 57.
- 9-month follow-up data

JNJ-3989	100 mg	200 mg	300 mg	400 mg
Mean (SE) HBsAg nadir	1.72 (0.18)	1.79 (0.14)	2.04 (0.20)	1.90 (0.18)
≥1.0 $\log_{10}$ HBsAg reduction at nadir from Day 1, n (%)	**39 (98) (range 1.11–3.77)**			



CONCLUSION

- JNJ-3989 (100–400 mg) with an NA was **well tolerated** in patients with CHB
- A ≥1.0 $\log_{10}$ reduction in HBsAg at nadir was achieved in **98%** of patients
- A subset of patients had **sustained HBsAg suppression** ~9 months after the last RNAi dose
  - Studies of longer term **dual therapy** (48 wks) and **triple therapy** including a CAM are underway

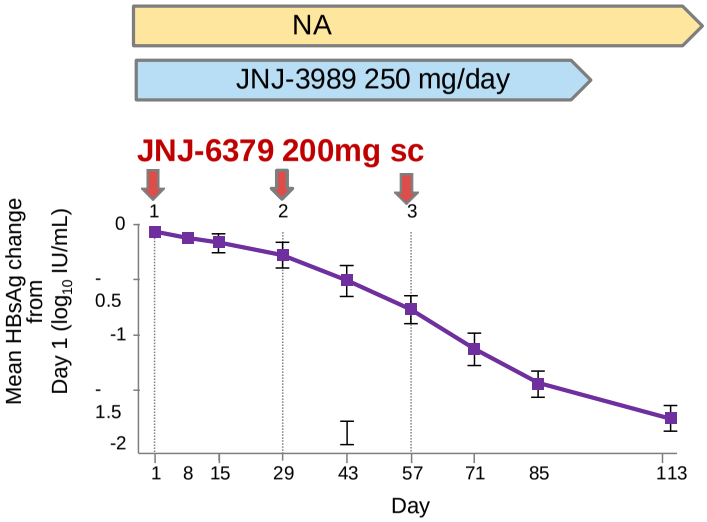
Gane EJ, et al. DILC 2020; GS10

Triple therapy: siRNA plus CAM plus NA for 12 weeks

12 eAg+/eAg- CHB patients, 7 NA treated and 5 NA naive

- **JNJ-3989 (siRNA) 200 mg: 3 sc doses on Days 1, 29 and 57**
- **Oral JNJ-6379 (CAM) 250 mg once daily for 12 weeks (until Day 85)**
- **ETV or TDF**

- Triple therapy resulted in marked decline in HBsAg levels
  - all pts achieved >1 log IU/ml reduction in HBsAg
- All pts showed rapid decline of HBV DNA up to 8 logs and of HBV RNA up to 7 logs
- Well tolerated

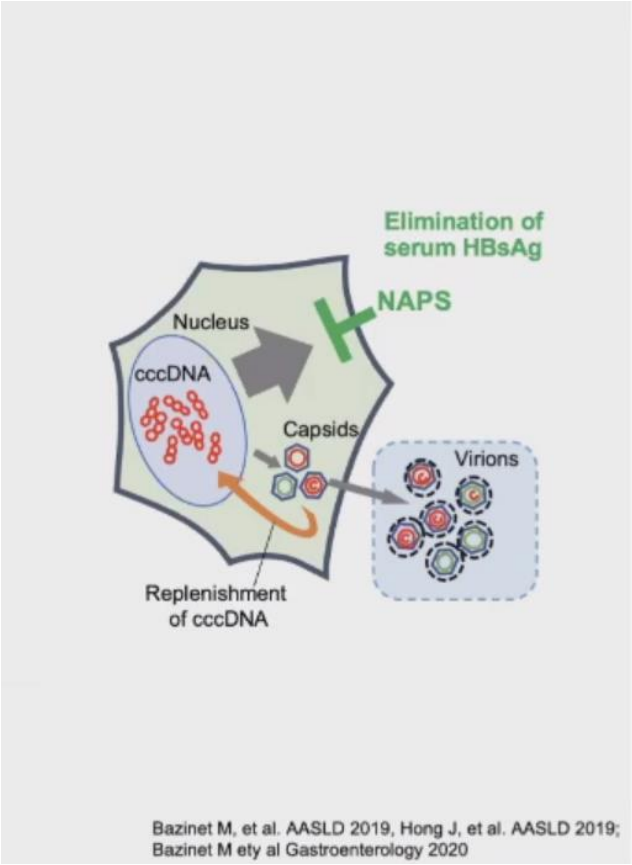


Next studies will be 48 weeks

Yuen M-F, et al. #LP4 AASLD 2019

HBsAg release inhibitors: Nucleic Acid Polymers (NAP's)

- Molecular target: HBV subviral particles (assembly/release)
- MoAs:
  - Exact mechanism of action not fully clear
  - Indirect immune modulation by reducing HBsAg (suggested by the association of ALT flares with response)
- Response often associated with several ALT flares
- Active against HBV and HDV

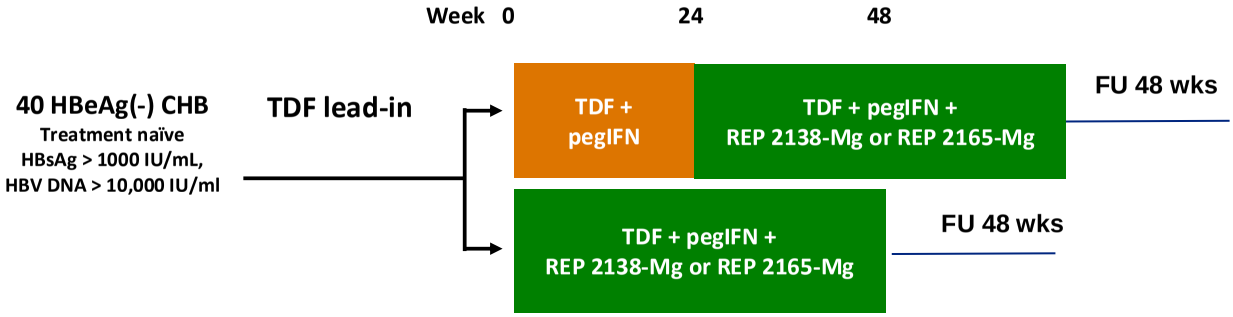


Bazinet M, et al. AASLD 2019, Hong J, et al. AASLD 2019; Bazinet M ety al Gastroenterology 2020

Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

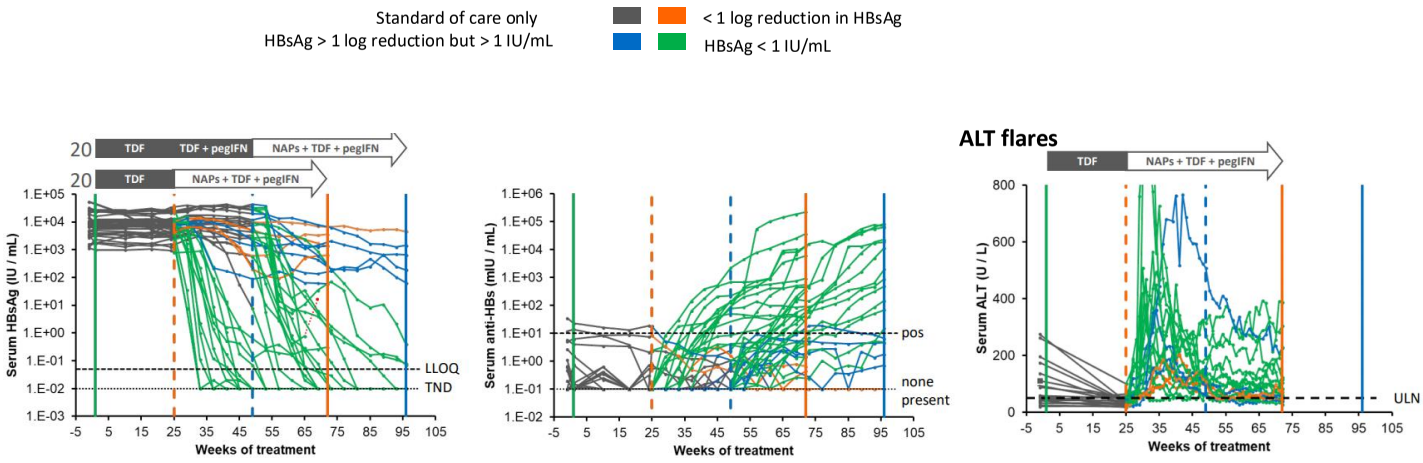
REP 401
Study

- **NAP (REP 2139-Mg or REP 2165-Mg 250 mg IV qW)** in combination with TDF and Peg-IFN for HBeAg-Negative CHB
- REP 2165 = REP 2139 variant with improved tissue clearance



Bazinet M, et al. Gastroenterology 2020

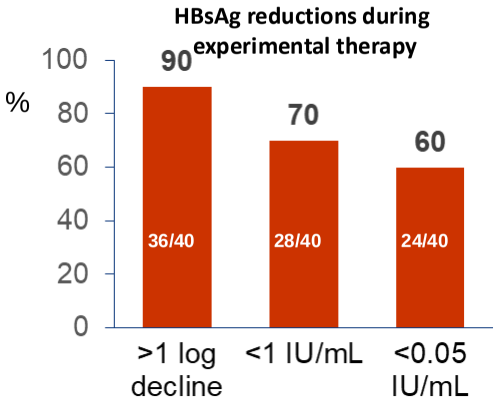
Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

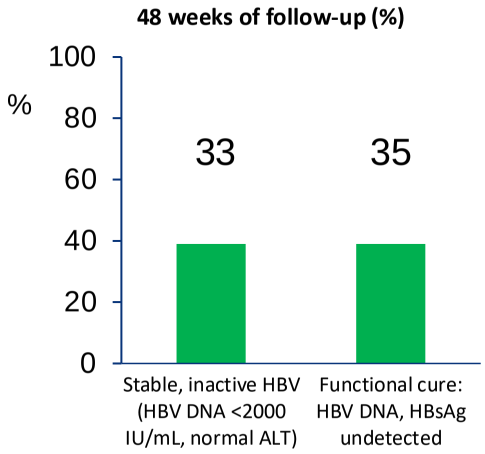


95% of pts experienced ALT flares during therapy

Bazinet M, et al. Gastroenterology 2020

Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

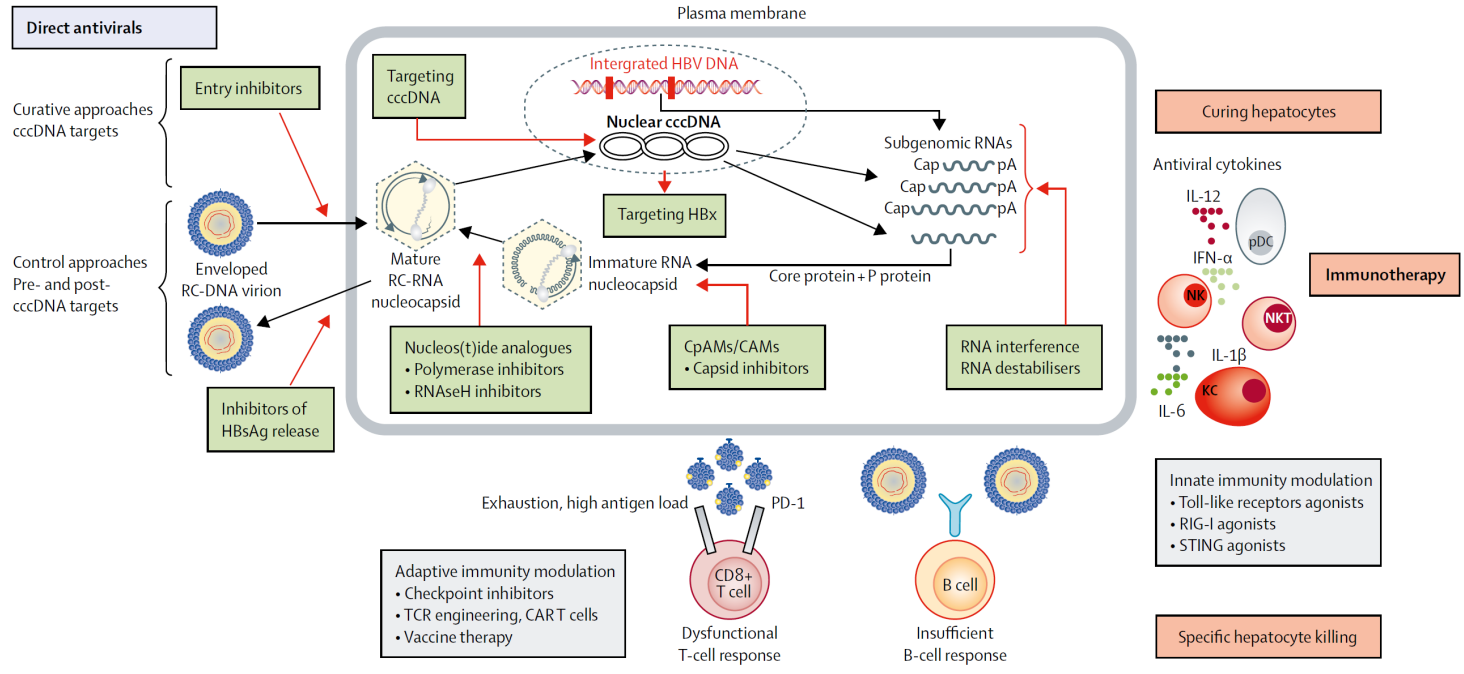




- Marked HBsAg reduction/clearance in combination with pegIFN and TDF, with high titered anti-HBs seroconversions
- ALT flares very common: Safety in cirrhotics?
- **Clinical benefit, no therapy required: 68% of patients**

Bazinet M, et al. Gastroenterology 2020

Current and future HBV virological and immunological targets for treatment and cure of CHB



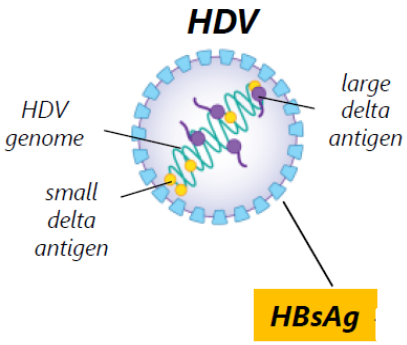
Revill PA et al. Lancet Gastroenterol Hepatol 2019

Le opzioni terapeutiche future per HBV

Summary

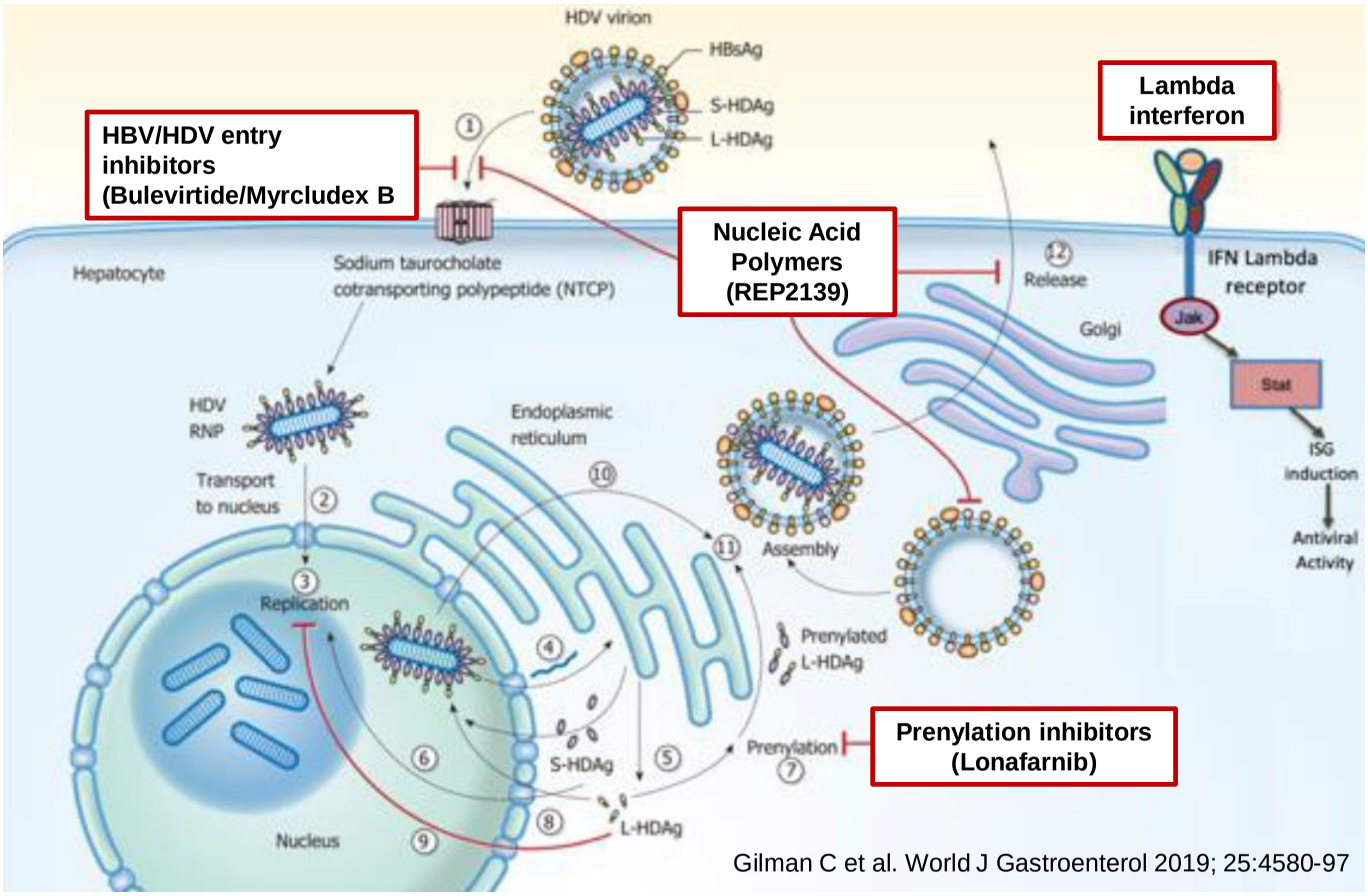
- HBV functional cure: end-point of future therapies
- Many promising therapeutic approaches to achieve HBV cure are currently evaluated in clinical trials
- Optimal combination unknown
  - Upcoming clinical trials will establish which drugs combinations may contribute to a functional cure

Hepatitis D (delta) Virus



- Defective virus that needs HBsAg for its propagation
- 15-20 million individuals are anti-HDV positive
- 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*
- No FDA or EMA approved therapy (NUC not effective, IFN for selected patients with only 20% off treatment virological response)
- New effective therapies are needed

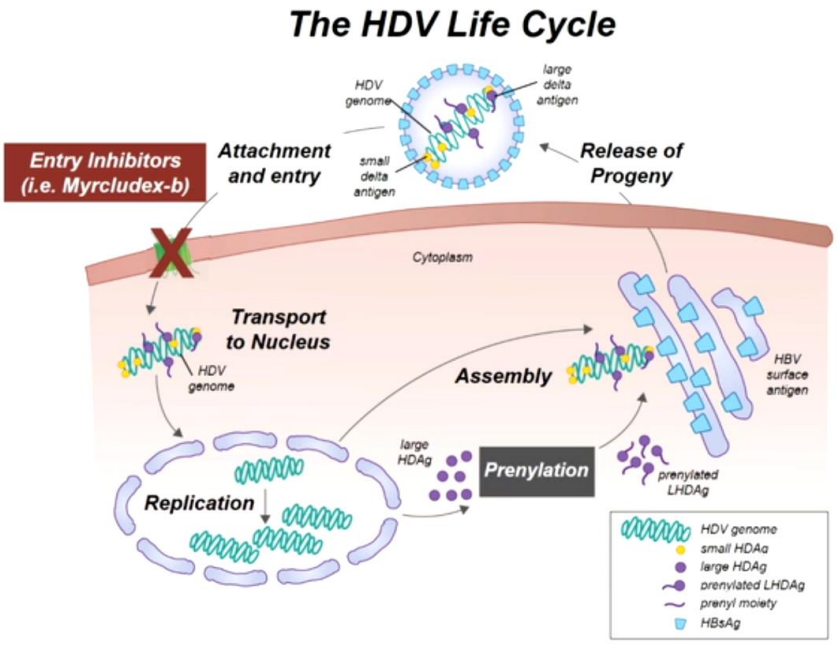
New treatment options for HDV:



Gilman C et al. World J Gastroenterol 2019; 25:4580-97

New treatment options for HDV:

Myrcludex B (MXB) or Bulevirtide (BLV)



Modified from Elazar M &Glenn J Curr Opin Virol 2018

Mode of action:

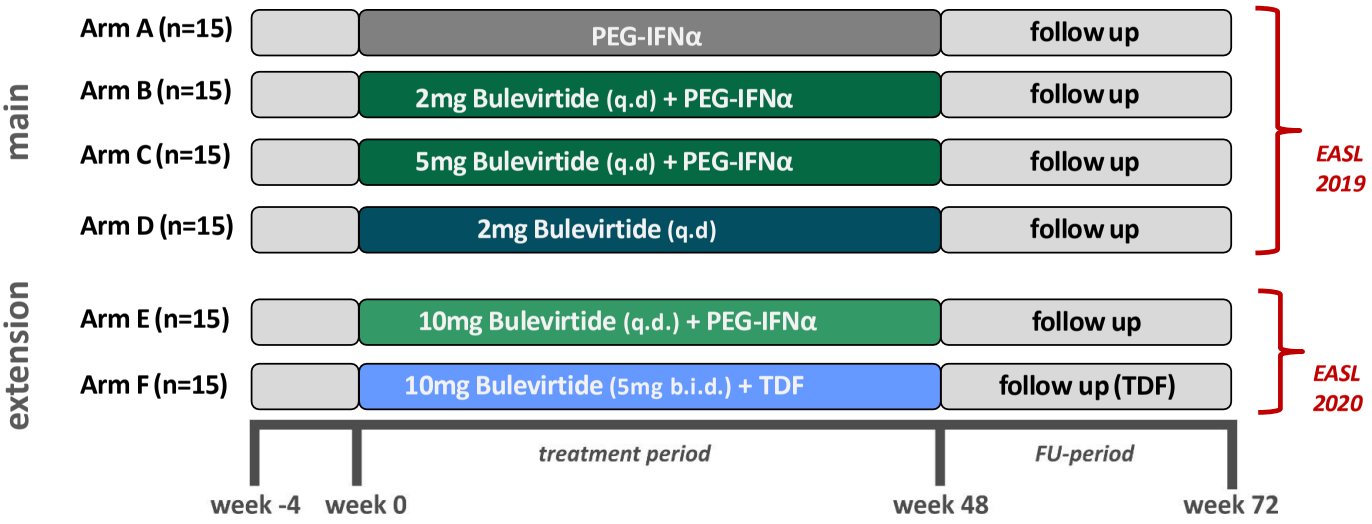
- BLV blocks NTCP, the entry receptor for HBV/HDV
- Hence, new infections are prevented
- Infected hepatocytes are replaced by naive cells, which will be protected from infection
- Consequently, viral spread in the liver is prevented

Administration:

- Self administered s.c injections
- Every day

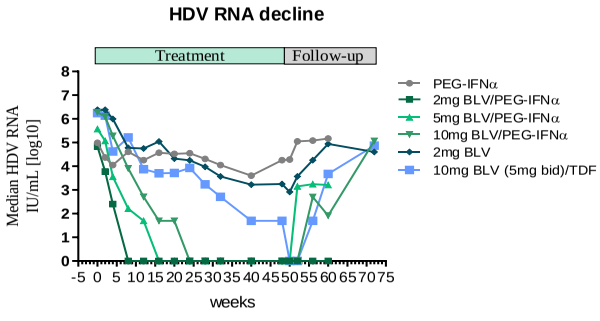
48-week bulevirtide mono or with PEG-IFN alfa-2a in CHD MYR203 phase 2 Main and Extension Study

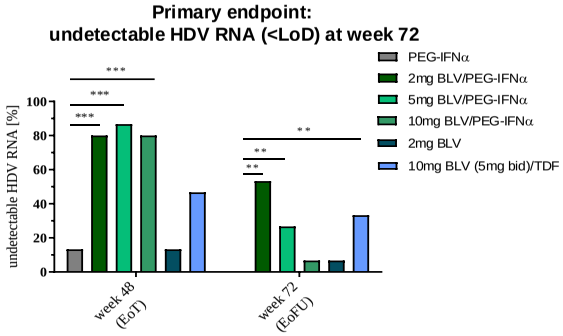
- 90 patients with chronic HBV/HDV coinfection were randomized into 6 treatment arms
- MyrB was self administered by patients once daily or b.i.d subcutaneously

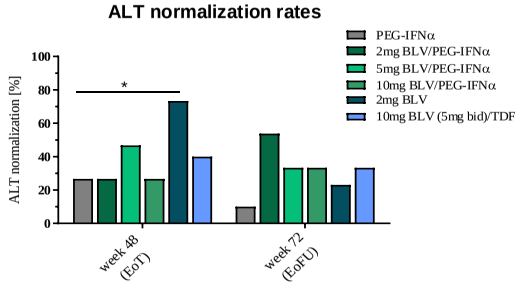


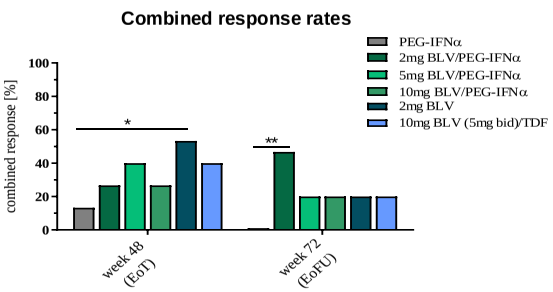
Wedemeyer H et al, EASL 2019 and 2020

48-week bulevirtide mono or with PEG-IFN alfa-2a in CHD MYR203 Main and Extension Study







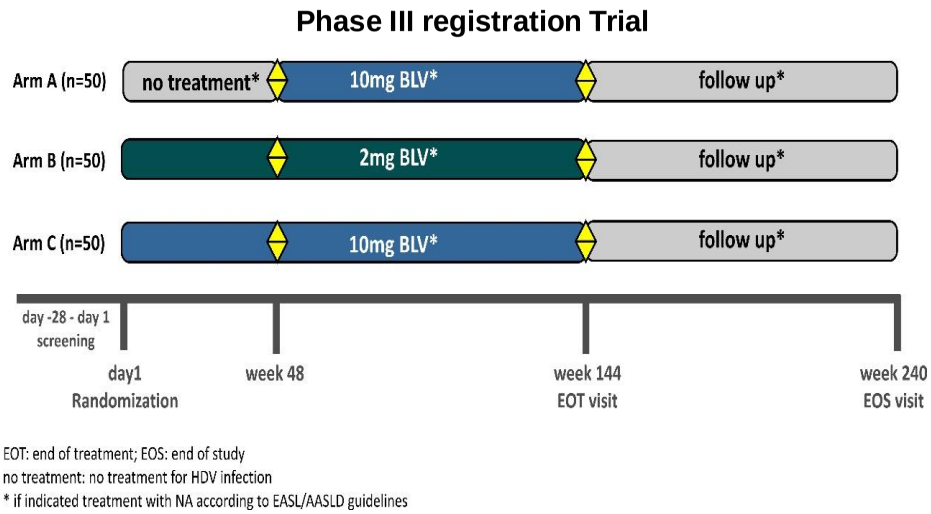


Combined response: undetectable HDV RNA or ≥2log$_{10}$ decline and ALT normalization
p≤0.05; p**≤0.01; p***≤0.001*

Conclusions:
Promising results but short-term treatment (48-week) requires combination of MXB (2 mg?) and PEG-IFN

Wedemeyer H et al, EASL 2019 and 2020

Myrcludex B (MXB) or HEPCLUDEX® for CHD



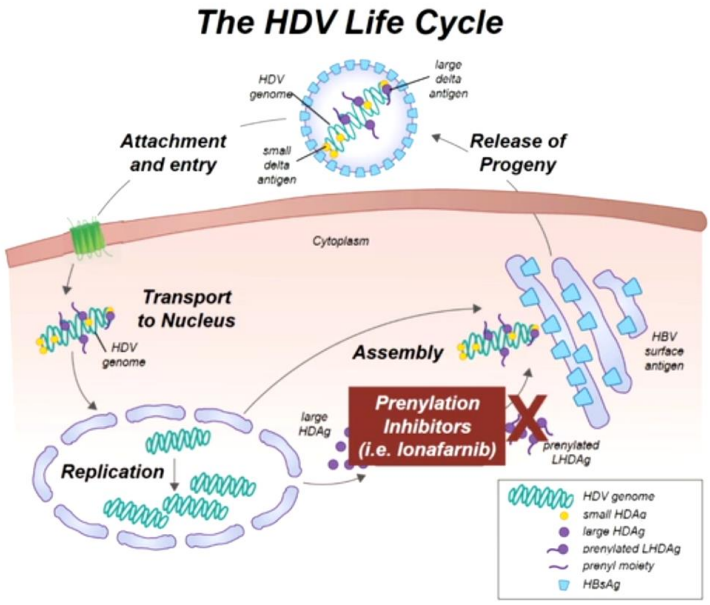
EOT: end of treatment; EOS: end of study
no treatment: no treatment for HDV infection
* if indicated treatment with NA according to EASL/AASLD guidelines

Study design

- International multicenter study
- 150 patients with CHD, monotherapy with BLV
- 6 countries: Germany, USA, Sweden, Italy, Georgia, Russia
- **Primary endpoint:** undetectable HDV RNA or decrease by ≥2log$_{10}$ IU/mL and ALT normalization at week 48
- Enrollment closed

- MXB (Hepcludex 2 mg die) has been approved in Europe in July 2020 for compensated CHD
- Expected AIFA approval and reimbursement in Italy, end of 2021
- No compassionate use protocol available yet
- Clinical study protocol in decompensated cirrhotics under development

New treatment options for HDV:
Lonafarnib



- Small molecule, oral
- Prenylation inhibitor that inhibits attachement of prenyl lipid farnesyl (cellular target) to LHDAg
- Disruption of prenylation prevents the interaction with HBsAg and formation of secreted particles (HDV assembly)

Modified from Elazar M &Glenn J Curr Opin Virol 2018

New treatment options for HDV:
Lonafarnib

Presented EASL The Home of Hepatology 2018

COMPOSITE ENDPOINTS ACHIEVED IN PHASE 2

≥ 2 Log Decline or BLQ at Week 24 + Normalized ALT

- **All-oral:** Lonafarnib boosted with Ritonavir
  - 33% (6 of 18) patients ≥ 2 log decline or BLQ at Week 24
  - 47% (7 of 15) patients normalized ALT at Week 24
  - **Composite endpoint: 29% (4 of 14)**

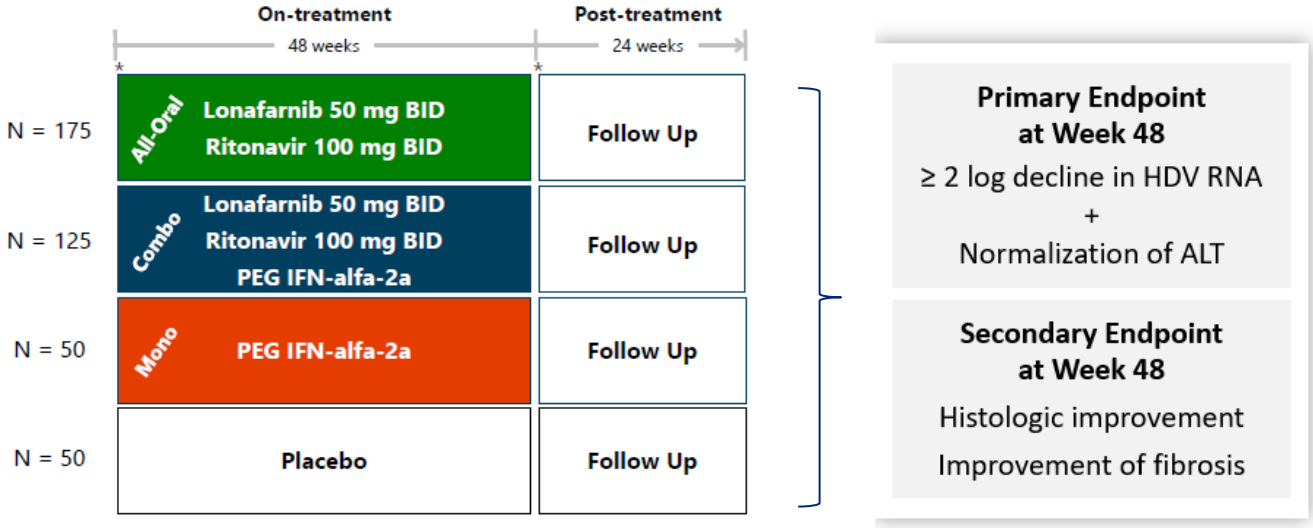
- **Combination:** Lonafarnib boosted with Ritonavir + PEG IFN-alfa-2a
  - 78% (7 of 9) patients ≥ 2 log decline or BLQ at Week 24
  - 88% (7 of 8) patients normalized ALT at Week 24
  - **Composite endpoint: 63% (5 of 8)**

- Predominant AEs were GI-related (mild / moderate)

Yurdayn et al J Hepatology 2018, abs PS-161

Lonafarnib Boosted with Ritonavir ± Peg-IFN a2a vs Peg-IFN a2a in patients with CHD: *A phase 3 study international study*

D-LIVR

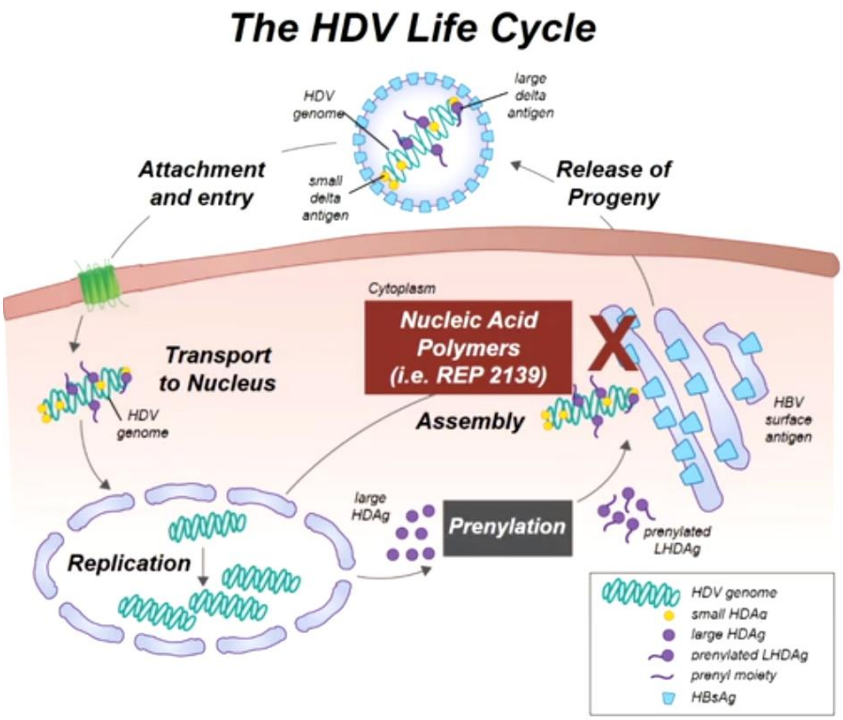


12 centers in Italy, enrollment still open, extended to 2021 !

* biopsy

All patients will be maintained on background HBV nucleoside therapy

New treatment options for HDV:
Nucleic Acid Polymers (NAPs)



Modified from Elazar M &Glenn J Curr Opin Virol 2018

- **NAPs are oligonucleotides** with broad spectrum in vitro antiviral activity
- **Molecular target:** HBV subviral particles (assembly/release)

REP 2139 and Peg-IFN in CHD patients
A phase 2 trial

Patients: 12 naive HBV/HDV coinfected patients without cirrhosis (HBeAg negative, HBsAg > 1000 IU/ml, HDV RNA positive)

Study design:

REP 2139-Ca
500 mg qW IV 15 weeks

REP 2139-Ca
250 mg qW IV 15 weeks

Pegylated interferon α-2a
180µg qW SC 48 weeks

Efficacy:

	EOT	1 year FU
HBsAg <50IU/ml	6/12	5/12 (42%)
HDV RNA negative	9/12	7/12 (58%)

Safety: Combined REP 2139 and Peg-IFN was safe, side effects attributed to Peg-IFN tossicity

Bazinet et al . Lancet Gastroenterol Hepatol 2017

An open label Phase 2 study of peginterferon lambda, lonafarnib and ritonavir for 24 weeks: end-of-treatment results from the LIFT HDV study

Treatment: 24 weeks LNF+RTV+PegIFN Lambda 180 ug/wk

- TDF or ETV started prior to therapy

RESULTS

- 26 patients completed therapy

Patient characteristics	
Male, %	65
Median age, years	40
Ethnicity, % Asian Caucasian Black	 54 31 15
Median baseline evaluations	
Aminotransferases ALT, IU/mL AST, IU/mL	 64 47
Ishak fibrosis score	3
Modified HAI inflammation	9
Virological markers HBV DNA, IU/mL Log HDV RNA, IU/mL	 <21 4.7

HDV RNA	After 12 weeks	After 24 weeks
Decline from BL, log IU/mL, median (IQR)	3.4 (2.9−3.8) p<0.0001	3.2 (2.5−4.0) p<0.0001
>2 log decline, n (%)	–	25 (96%)
Undetectable or <LLOQ, n (%)	7 (27)	11 (42%)
<LLOQ, n (%)	6 (23)	3 (11%)

- AEs were mostly mild to moderate*
- Dose reductions in 3 patients and treatment discontinuation in 4 (15%) patients

CONCLUSION

- LMD/LNF/RTV in chronic HDV patients appears to be safe and well tolerated for up to 6 months in most patients
- After 24 weeks, almost all achieve >2 log decline in HDV RNA, with >50% achieving undetectable or <LLOQ HDV RNA levels
- Results support continued exploration of this triple therapy in HDV

- *Including GI-related side effects, weight loss, hyperbilirubinaemia, and anaemia

Koh C, et al. EASL 2020; LBP13

New treatment options for HDV

Summary

- New drugs under development: HDV specific or HBV specific
- Two phase III studies ongoing also in Italy (MXB mono and IFN±LNF+RTV)
- Hepcludex (MXB) will be approved by AIFA by the end of 2021
- A clinical study in decompensated patients will start in 2021