***Identification of a novel deltavirus in Boa constrictor***

**Udo Hetzel et al ,in press**

*A divergent hepatitis D-like agent in birds 2*

Michelle Wille  et al, -Viruses  2018

Prevalence and burden of **hepatitis D** virus Infection in the global population:
a systematic review and meta-analysis. ,

Chen HY e al, Gut 2018

anti-HD+ worldwide :

10.5% of all HBsAg positive

# TASHKENT , UZBEKISTAN

**The number of patients diagnosed with CVH B, CVH C, CVH B + D and hepatic viral cirrhosis which hospitalized and treated in the hospital based of the Research Institute of Virology for the period 2015-2018 years.**

| № | Nosology | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|
| 1 | Chronic Viral Hepatitis C | 684 | 561 | 435 | 550 |
| 2 | Chronic Viral Hepatitis B | 240 | 229 | 221 | 248 |
| 3 | Chronic Viral Hepatitis B+D | 226 | 187 | 204 | 281 |
| 4 | Chronic Viral Hepatitis B+C | 20 | 24 | 15 | 22 |
| 5 | Chronic Hepatitis non-viral etiology | 83 | 87 | 64 | 94 |
| 6 | Liver Cirrhosis with HCV etiology | 843 | 947 | 912 | 1036 |
| 7 | Liver Cirrhosis with HBV etiology | 199 | 233 | 196 | 193 |
| 8 | Liver Cirrhosis with HBV+HDV etiology | 382 | 831 | 914 | 1206 |

# The HDV target : problems

- HBV required only to provide the HBsAg capsid

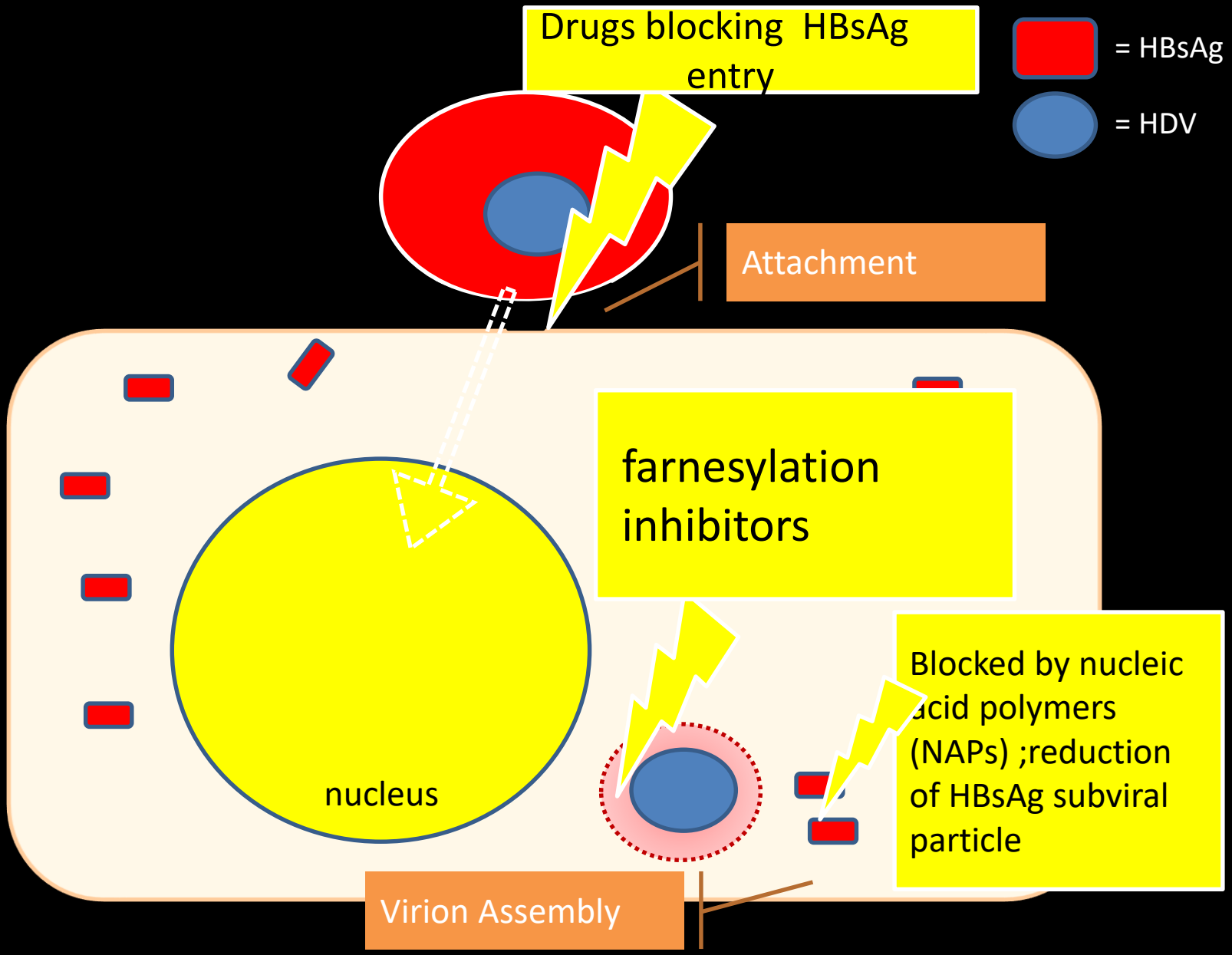
- replication of HDV indipendent from HBV DNA replication

NO REPLICATIVE FUNCTION OF HDV TO BE TARGETED BY ANTIVIRALS

# New therapeutic strategies against the HDV

targeted to deprive the HDV of functions critical to its life-cycle , provided by the HBV or by the hepatocyte

# HDV: new therapeutic targets



# OPTIONS IN CLINICAL EVALUATION

the inhibition of the export of the HDV by the nucleic acid polymer REP 2139 through the presumed interference with the synthesis of subviral HBsAg particles

the disruption by Lonafarnib of the farnesylation of the large HD-antigen required for virion morphogenesis

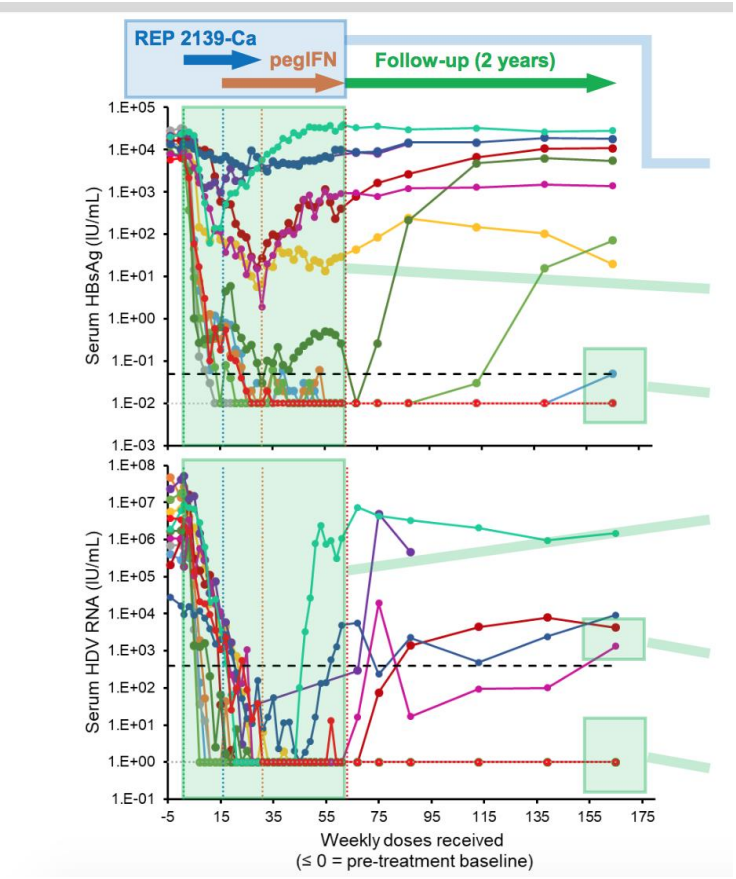
the block of HDV entry into hepatocytes by the synthetic peptide Myrcludex B

….all in combination with PEG-IFN alfa….

-.

REP 2139

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




HBsAg response in 75%, loss in 42%,

Follow-up:HBsAg control in 45%

HDV RNA decline > 5 log in all,
92% achieve HDV-RNA TND

Follow -up: 7/11 maintain HDV-RNA TND

TND =Target not detected

*Bazinet et al., 2017*

# REP 2139, ?

mechanism of action:

limited evidence supports the assumption that the drug clears HD viremia by blocking the release of HBsAg and subviral HBV particles - Vaillant A. et al. Antiviral Res 2016

NAPS but not REP 2139) inhibit HDV entry in human hepatoma cells ( by preventing attachment to cell surface glycosaminoglycans ?- Beilstein F. et al . J Virol, 2018

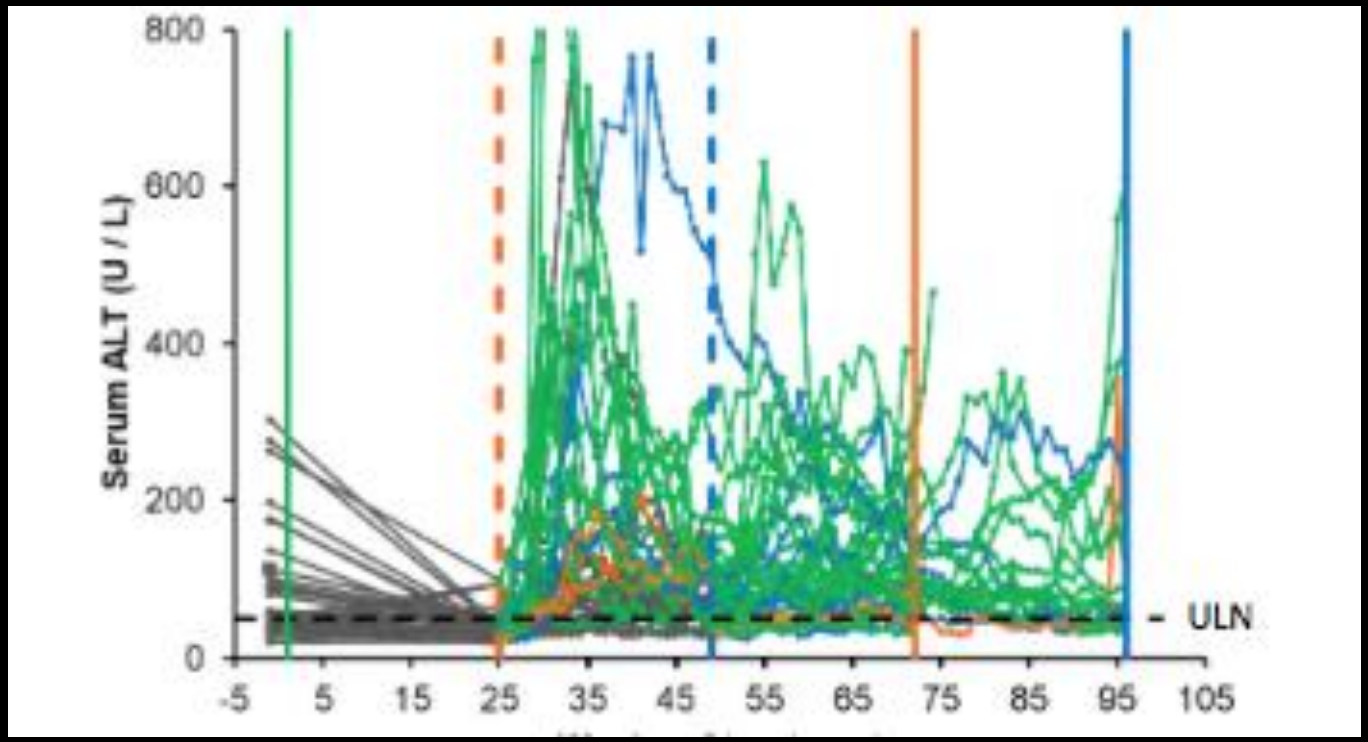
accumulation of HBsAg in cytoplasm ?- increased risk of HCC ?

binding to cell proteins containing amphipatihic helixes (lipoproteins)

administration currently too demanding

ALT elevations ?

ESTABLISHMENT OF HIGH RATES OF FUNCTIONAL CONTROL AND REVERSAL OF FIBROSIS FOLLOWING TREATMENT OF HBeAg-NEGATIVE CHRONIC HBV INFECTION WITH REP 2139 -MG/REP 2165- Mg, TENOFOVIR DISOPROXIL FUMARATE AND PEGYLATED INTERFERON- alpha 2a M. Bazinet et al , AASLD 2018




- **ALT flares occur in ~ 90% of patients and are likely therapeutic in nature:**
- **Self resolving**
- **Otherwise asymptomatic (even in patients with advanced fibrosis)**
- **Correlated with antiviral responses and establishment of functional control off therapy**

LONAFARNIB

# LONAFARNIB (LNF) PERSPECTIVES

To date, 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, against HDV . 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-- )

# LONAFARNIB (LNF) PERSPECTIVES

*most promising regimens for long term use :*

LNF 50 mg with Ritonavir 100 mg - twice daily orally

LNF 25 mg with Ritonavir 100 mg- twice daily orally-,plus PEG IFN alfa

*side effects ameliorated but still relevant*

*accumulation of HDV-RNA in liver cells ?*

**Eiger Announces PRIME Designation Granted by European Medicines Agency for Lonafarnib for Treatment of Hepatitis Delta Virus Infection**

**Phase 3 HDV "D-LIVR" International Study Initiating**

2018

**Eiger BioPharmaceuticals Announces Positive Phase 2 LIMT Study End of Treatment Data with Pegylated Interferon Lambda Monotherapy in Hepatitis Delta Virus (HDV) Infection**

- **Lambda Antiviral Activity Demonstrated in HDV Infection**

# MYRCLUDEX B

# Myrcludex B(Bulevirtide)

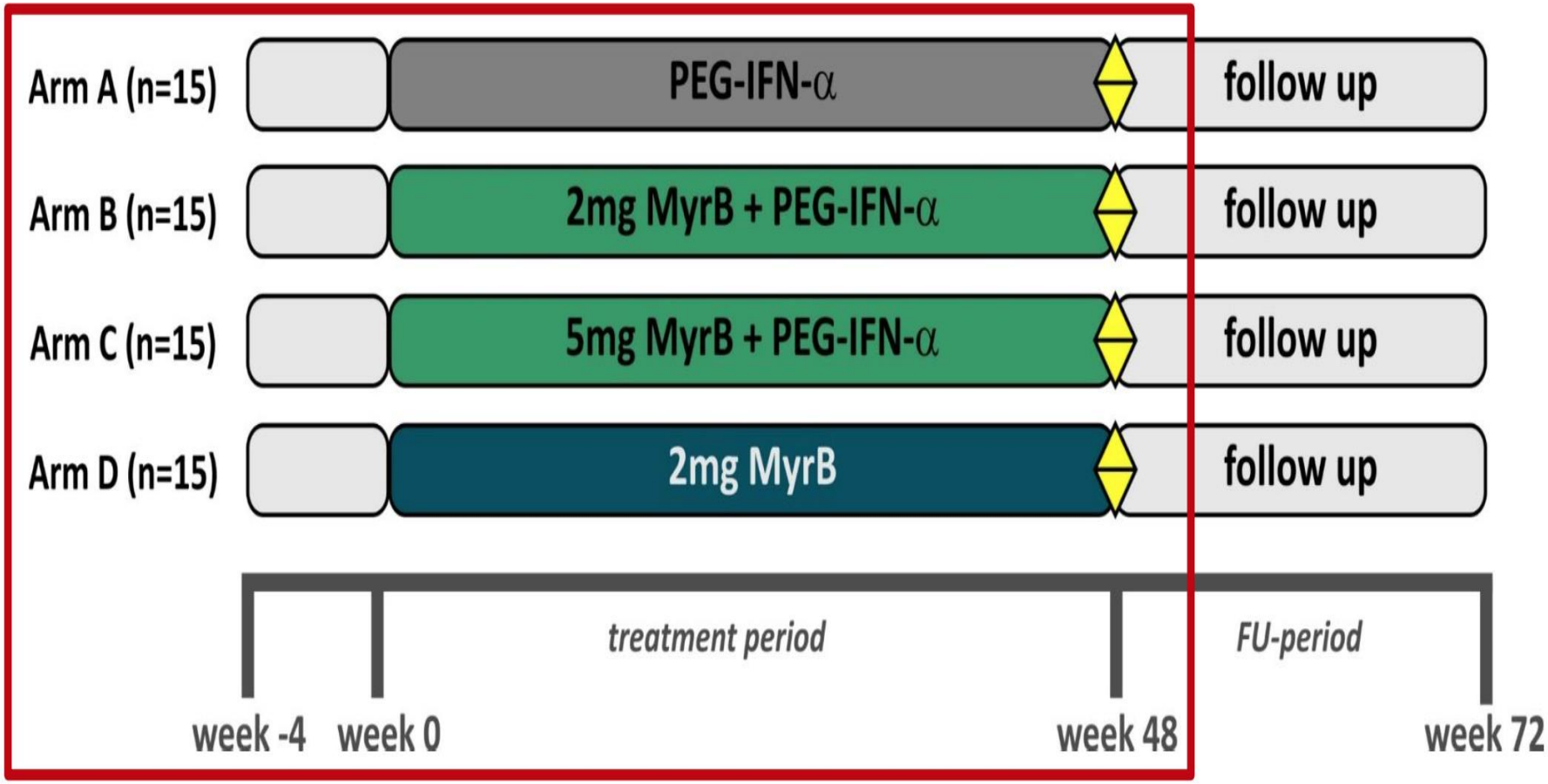
synthetic N-acetilated pre-S1 derived lipopeptide that inhibits HBV entry into hepatocytes in vitro and in vivo

*by blocking HBsAg entry ,Myr should prevent new infection of hepatocytes with HBV/HDV. Proliferating virus-free hepatocytes should recolonize the liver, eliminating HBV ccc-DNA and hepatitis D*

*Lemp FA and Urban S , 2014*

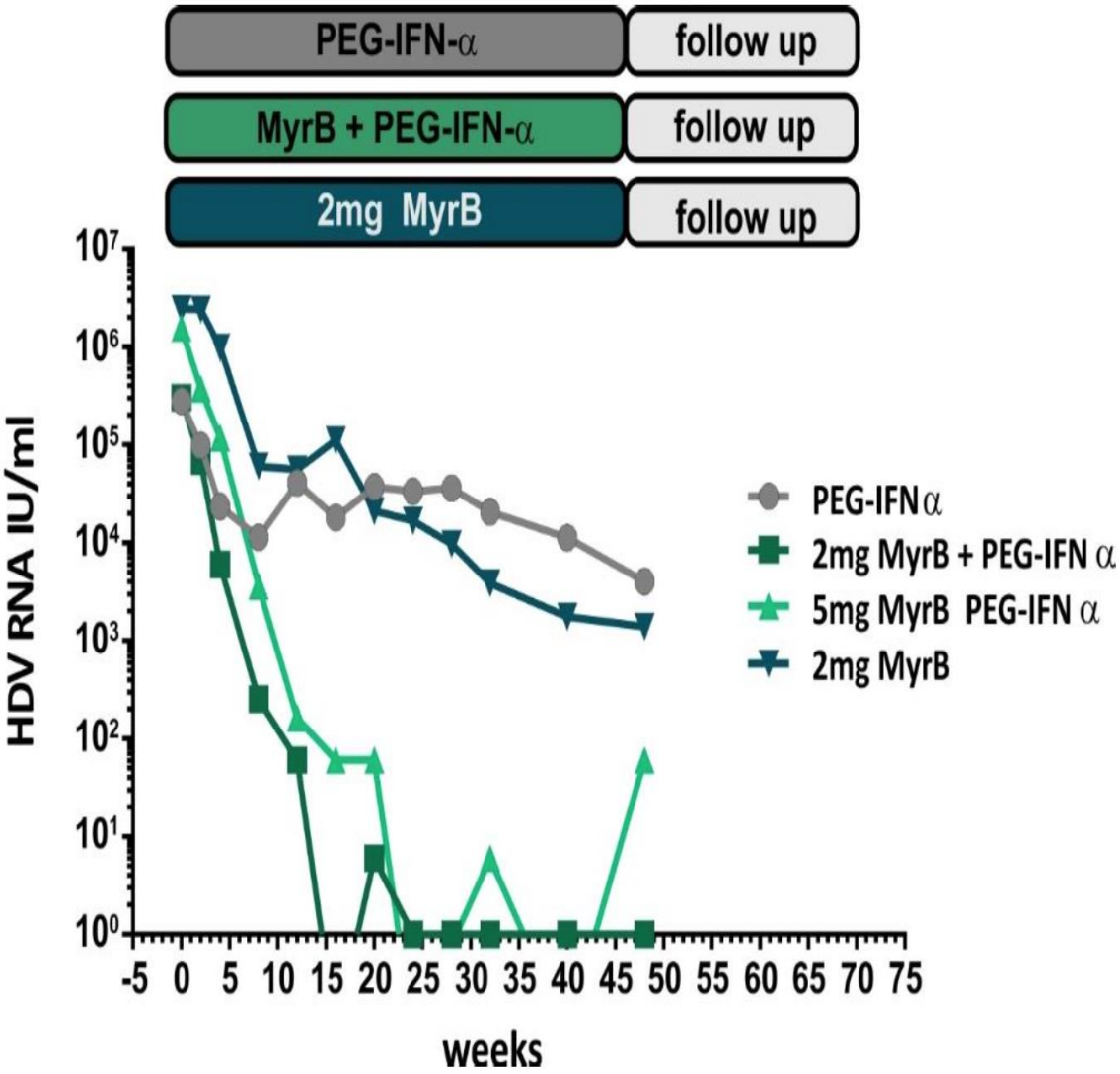
# MYR203 Study Design

- 60 patients with chronic HBV/HDV co-infection were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 15 patients per arm
- Myrcludex B was self administered by patients once daily s.c.



# Virological Response (HDV RNA)

## Median HDV RNA levels

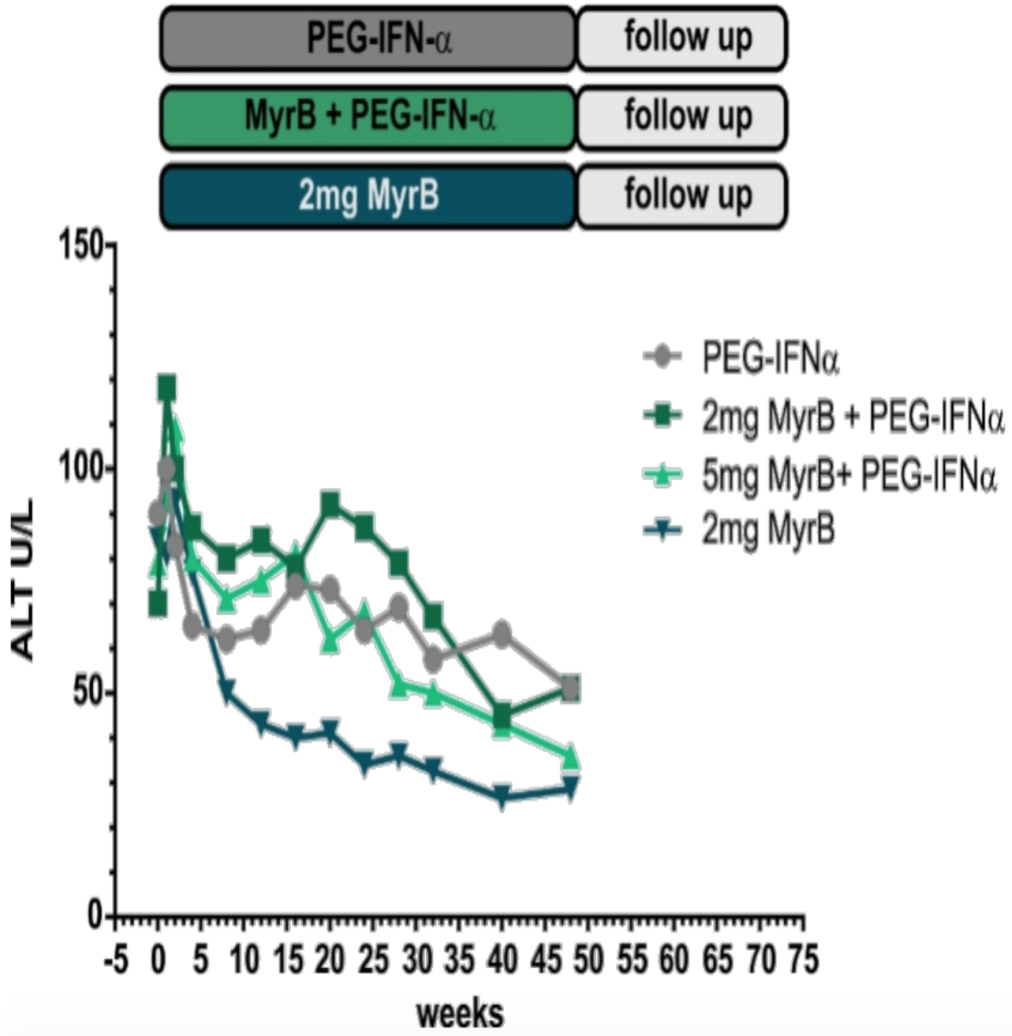



## Median RNA $log_{10}$ change to BL at week 48:

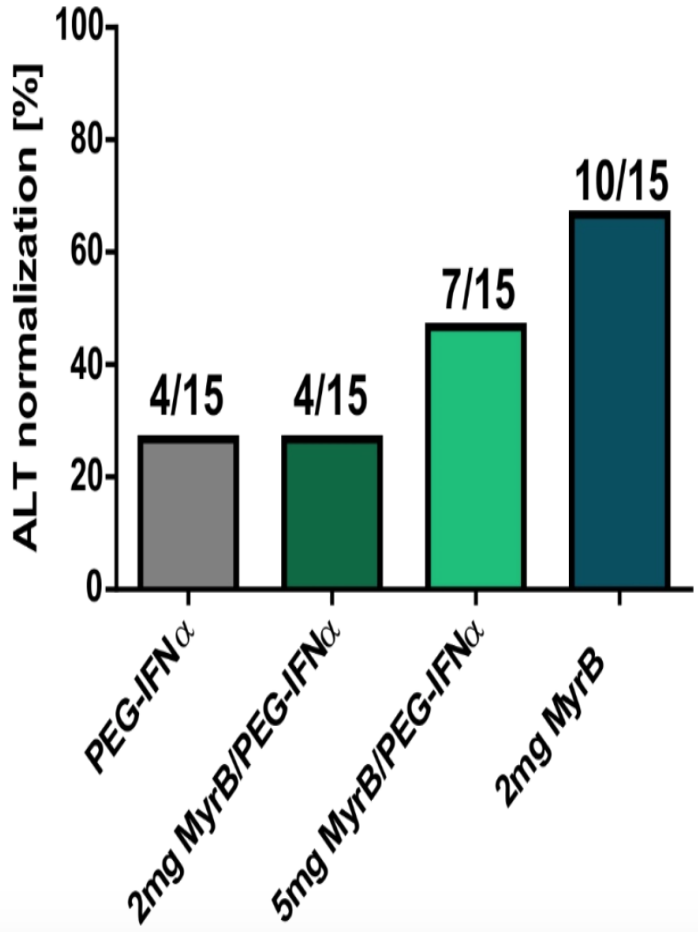
| | |
|---|---|
| 2mg MyrB/PEG-IFNα: | -3.62 |
| 5mg MyrB/PEG-IFNα: | -4.48 |
| 2mg MyrB: | -2.84 |
| PEG-IFNα: | -1.14 |

# Biochemical Response (ALT)

## Median ALT levels




## ALT normalization at week 48



- MYRCLUDEX B WITH PEG-IFN FOR 48 WEEKS

- distinct decrease of HDV-RNA (less with Myr 2mg only)
- distinct decrease of ALT (better with Myr 2mg only)
- no relevant biliary problem or side effect of Myr
- no major effetc on HBsAg

# WHAT ‘S NEXT ?

prolong therapy with the ultimate goal
of eradicating HDV/HBV.
for how long ?- PREDICTORS….. END POINT……

mantain remission of HDV RNA and ALT,
functional control of Hepatitis D ?

BY BLOCKING HBsAg ENTRY, MYR SHOULD PREVENT NEW INFECTION OF HEPATOCYTES WITH HBV/HDV ……

*HOWEVER :*

*HBV DNA integration is a crucial source of HBsAg -Wooddell, C. . 2017- HBsag from integrated HBV DNA may support HD Virion syhthesis - Freitas N, 2014- This might explain why Myrcludex B had a major effect on HBV DNA and HDV RNA but a minor effect on HBsAg levels.*

*HDV persists during liver regeneration by transmitting HDVRNA to dividing cells even in the absence of HBV coinfection - Giersch K , Gut 2019 –*

*This may explain why HDV clearance is difficult to achieve in HBV/HDV patients*

TREATING CHRONIC HEPATITIS DELTA:

THE NEED FOR SURROGATE MARKERS OF TREATMENT EFFICACY ,

Cihan Yurdaydin et al ,on behalf of the Hepatitis Delta International Network (HDIN)

....In conclusion, this panel of experts recommends a new virologic surrogate marker (i.e. ≥ 2log drop in HDV RNA), as the target for the assessment of initial treatment efficacy in clinical trials of novel therapies for patients with CHD.

J Hepatol, 2019 in press

# The devotion to surrogate outcomes in drug development for liver disease

Surrogate end points are often used in clinical trials where the time to clinical outcomes is long. In patients with liver disease, these surrogate outcomes are rarely validated. Without validation, treatment effects reported in trials might not directly translate to patient benefit after licensing.

|Rowe I.A *Nature Reviews Gastroenterology & Hepatology* ,2018

Dig.Liv.Dis 2018 Sep 21. pii: S1590-8658(18)30978-2.
doi: 10.1016/j.dld.2018.09.008.

***The present profile of chronic hepatitis B virus infection highlights future challenges: An analysis of the Multicenter Italian MASTER-B cohort.*** *Brancaccio G et al.*

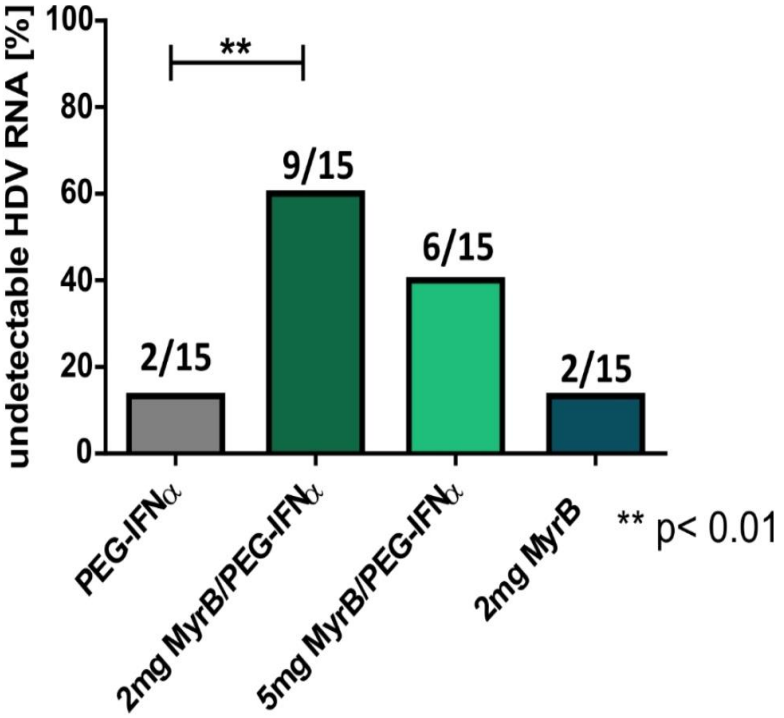
.....Among 2877 HBsAg positive individuals ,27% were non-Italian natives …Among NINs, age was younger, male gender was less prevalent and liver disease less advanced than in Italians .....

HDV coinfections 11.1% vs 7.3% (p = 0.006)...

Anti-HDV were detected more frequently in patients with cirrhosis. Fifty percent of NINs with cirrhosis were aged below 45 years.

# Virological Response (HDV RNA)

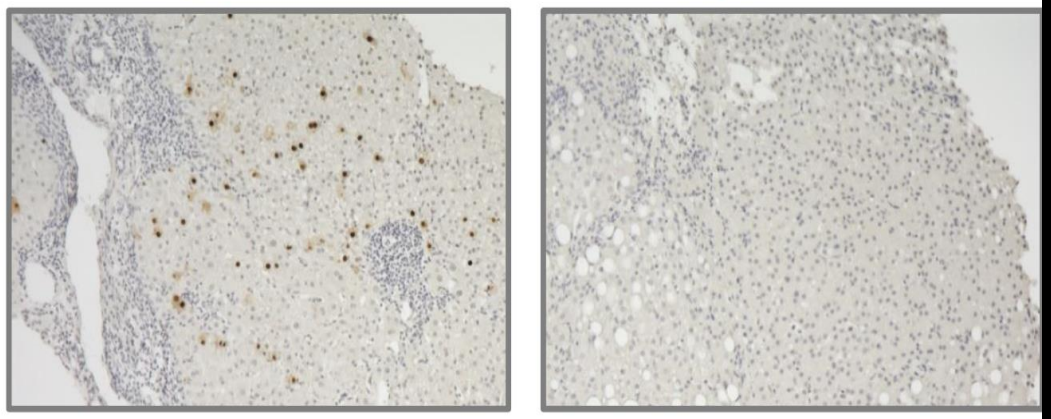
**Secondary endpoint: undetectable HDV RNA at week 48**




- Plasma HDV RNA decline correlated with intrahepatic decrease of HDV RNA replication and HDAg-positive cells

HDAg at baseline

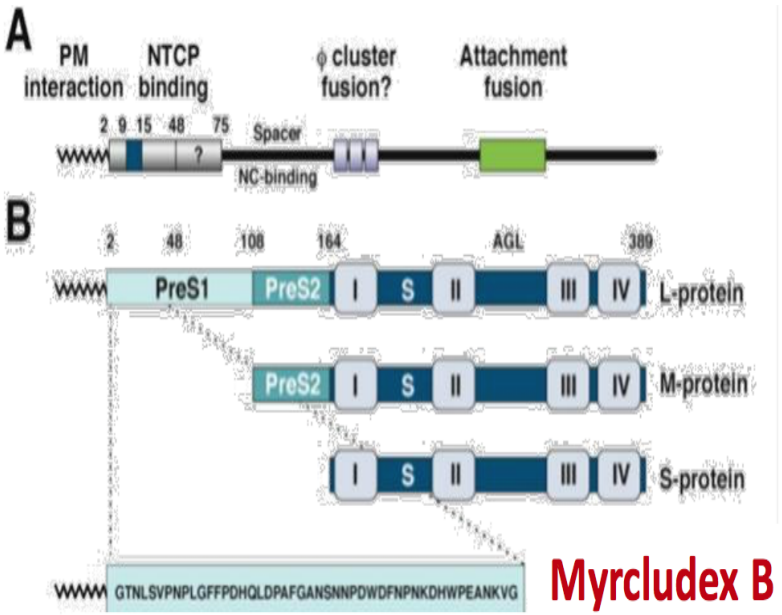
HDAg at week 48



*Arm B (01307): 2mg MyrB + PEG-IFNα*

HDAg; HE-stain

# Myrcludex B (Bulevirtide)




*Urban et al., Gastroenterology 2014*

- Specifically binds to sodium taurocholate co-transporting polypeptide (NTCP) at the basolateral membrane of differentiated hepatocytes *(Ni et al., Gastroenterology 2014)*
- Shows strong inhibitory potential for HBV/HDV infection ($IC_{50}$ ca 80 pM in PHH) *(Schulze et al., J. Virology 2010)*
- Exclusively targets parenchymal liver cells *(Schieck et al., Hepatology 2013)*

- Has been dosed to 272 hepatitis B and D patients and healthy subjects
- Induced HDV RNA declines in the MYR201-D trial *(Bogomolov et al.,Hepatology 2016)*
- Monotherapy induced HDV RNA declines and improvement in ALT levels in hepatitis D patients in the MYR202 trial (24 weeks of treatment) *(Wedemeyer et al., EASL 2018)*

…., we propose
to use in clinical trials as a surrogate marker for initial treatment efficacy, a decline of 2 or more logs of HDV RNA at end of treatment (duration of treatment may vary with different drugs used). We think that it is reasonableto assume that compounds achieving this antiviral effect can be an important adjunct to other drugs with different antiviral mechanisms in improving the management of CHD, provided that these compounds possess also a reasonable safety profile.

Yurdaydin C. J Hepatol ,in press , 2019

BY BLOCKING HBsAg ENTRY, MYR SHOULD PREVENT NEW INFECTION OF HEPATOCYTES WITH HBV/HDV .
PROLIFERATING VIRUS-FREE HEPATOCYTES SHOULD RECOLONIZE THE WHOLE LIVER, ELIMINATING HBV CCC-DNA AND HEPATITIS D

*HOWEVER :*

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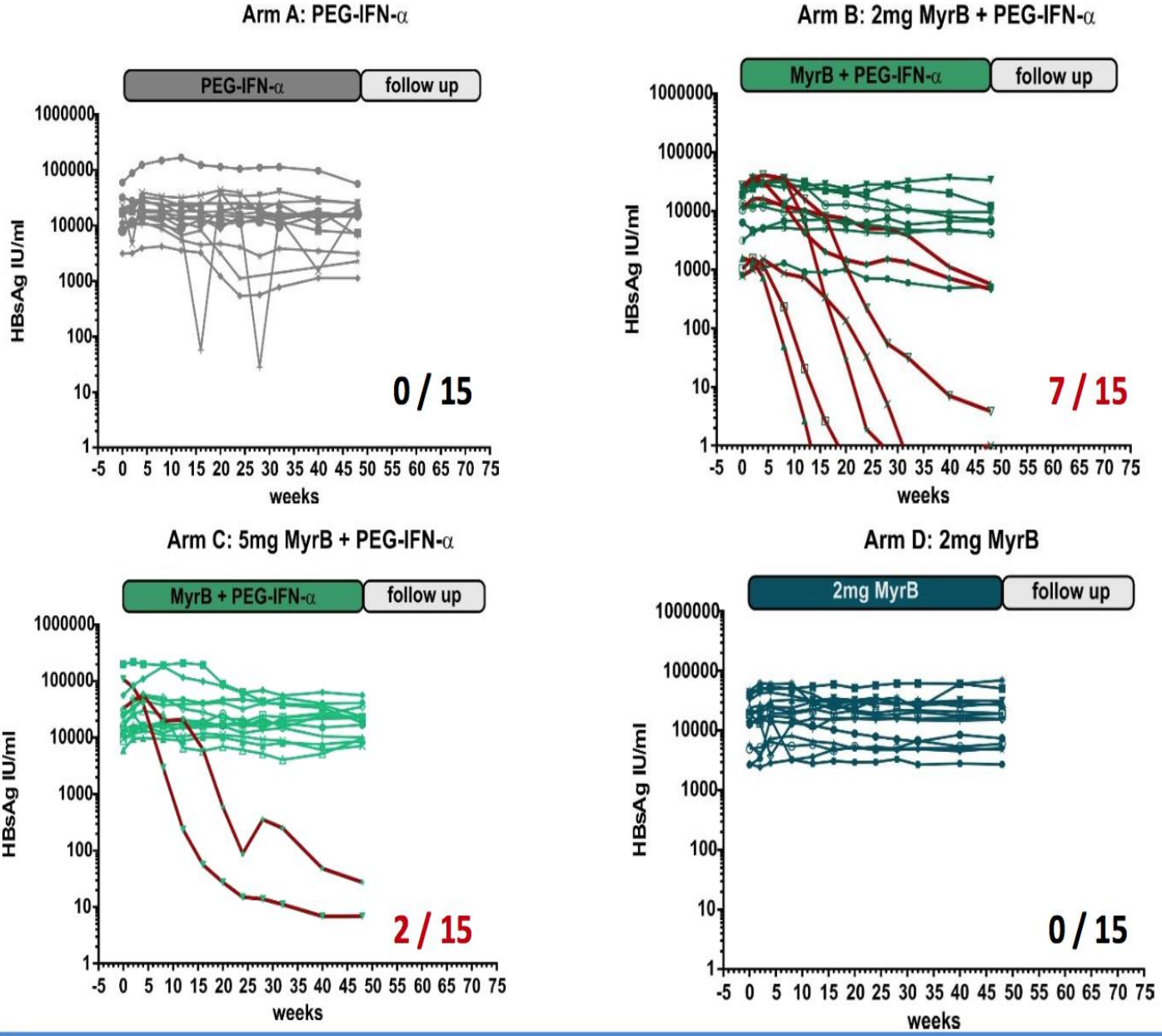
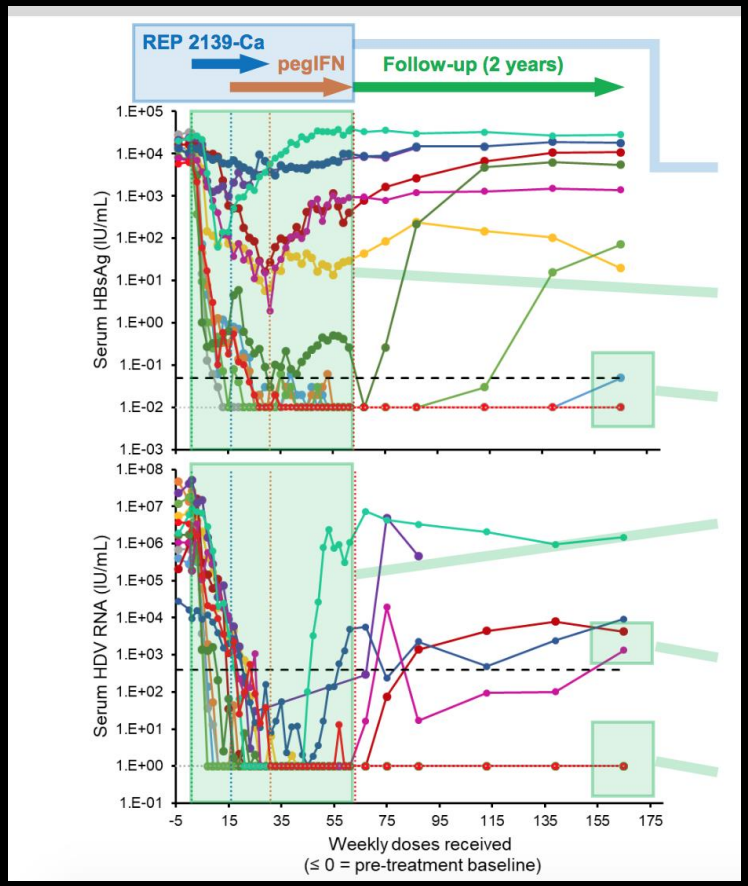
*As HBsAg from integrated HBV DNA may support HD Virion syhthesis - Freitas N, 2014- this might explain why Myrcludex B had a major effect on HBV DNAand HDV RNA but a minor effect on HBsAg levels.*

*HDV persists during liver regeneration by transmitting HDVRNA to dividing cells even in the absence of HBV coinfection - Giersch K , Gut 2019 -*
*The persistence capacities of HDV may explain why HDV clearance is difficult to achieve in HBV/HDV chronically infected patients.*

# HBsAg Response (≥1log$_{10}$ decline or undetectable)






HBsAg loss in 42%,
HBsAg control in 45%

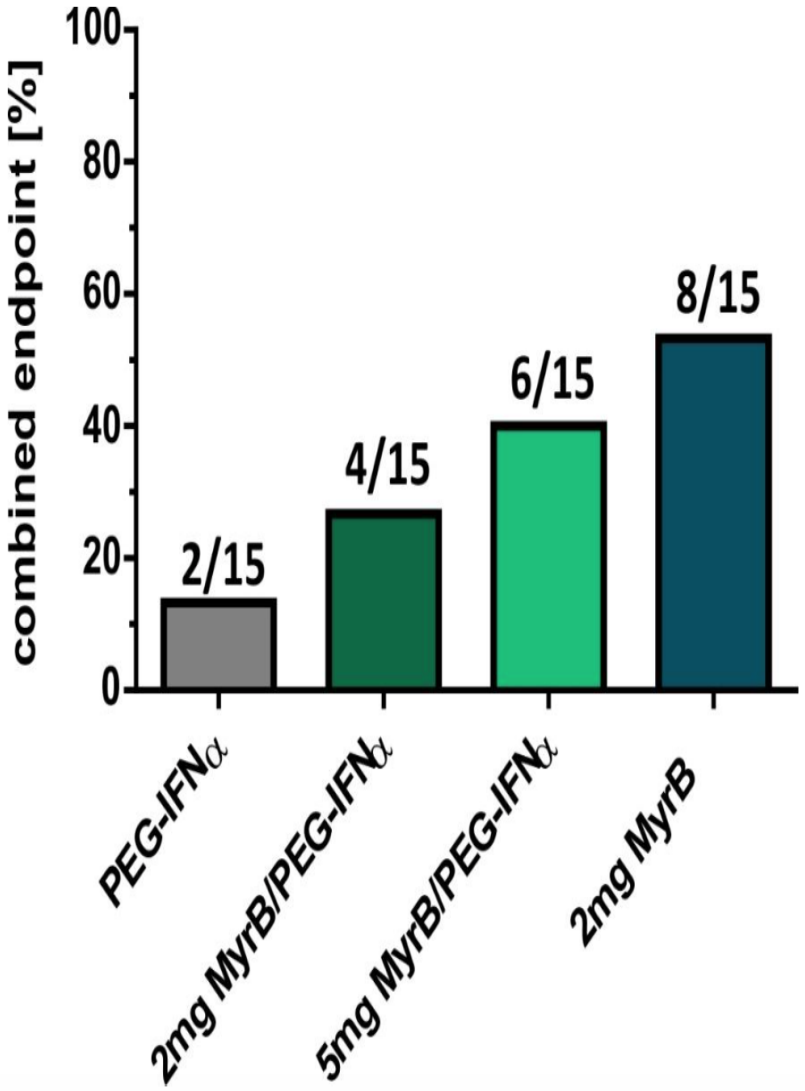
HDV RNA > 5 log $_{10}$
92%: achieve HDV RNA TND

Folow up: 7/11* maintain HDV RNA TND

# Combined Treatment Response at week 48

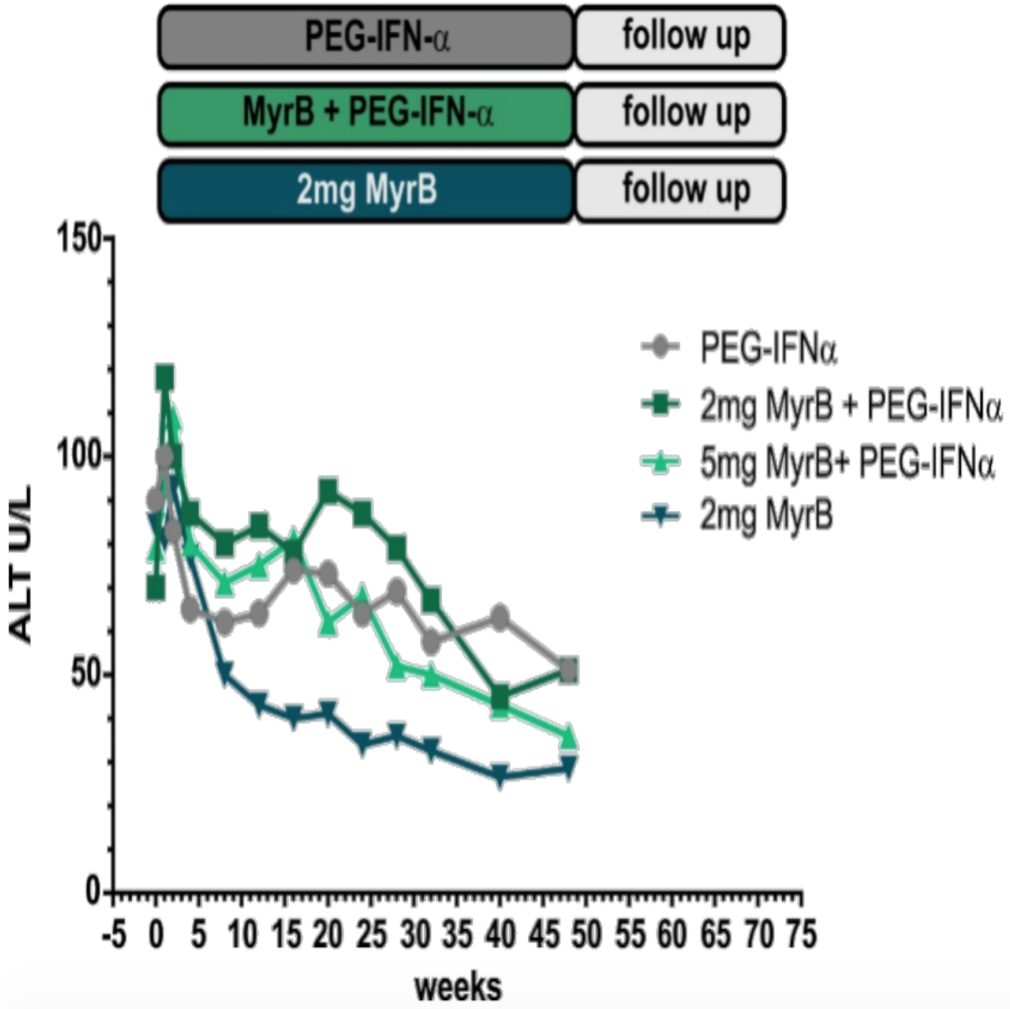
- Combined treatment endpoint agreed upon with FDA and EMA:

*"≥2log$_{10}$ IU/ml decline or undetectable HDV RNA (<LoD, target not detected) and normal ALT values"*

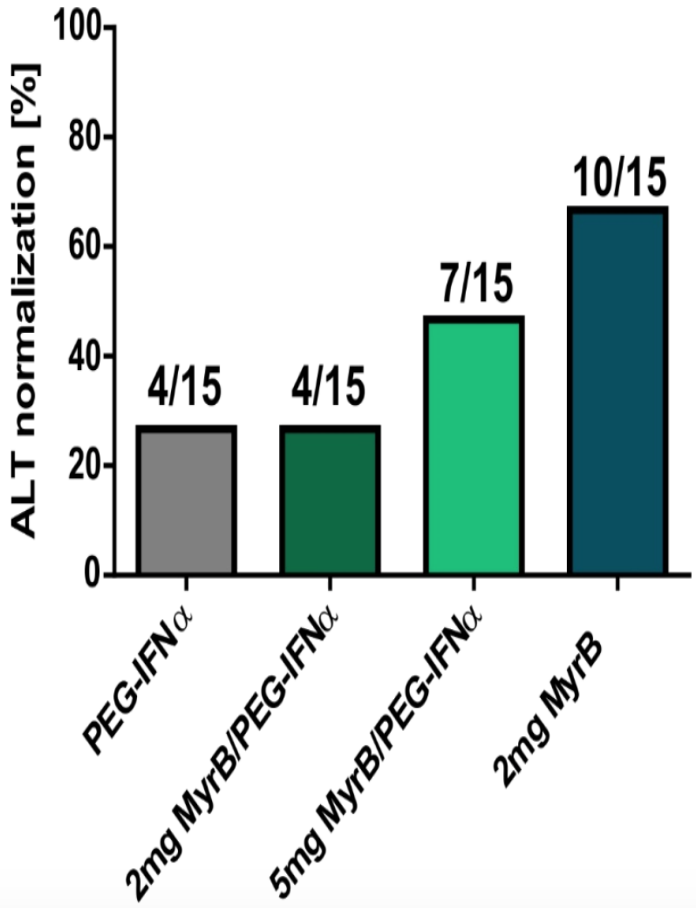


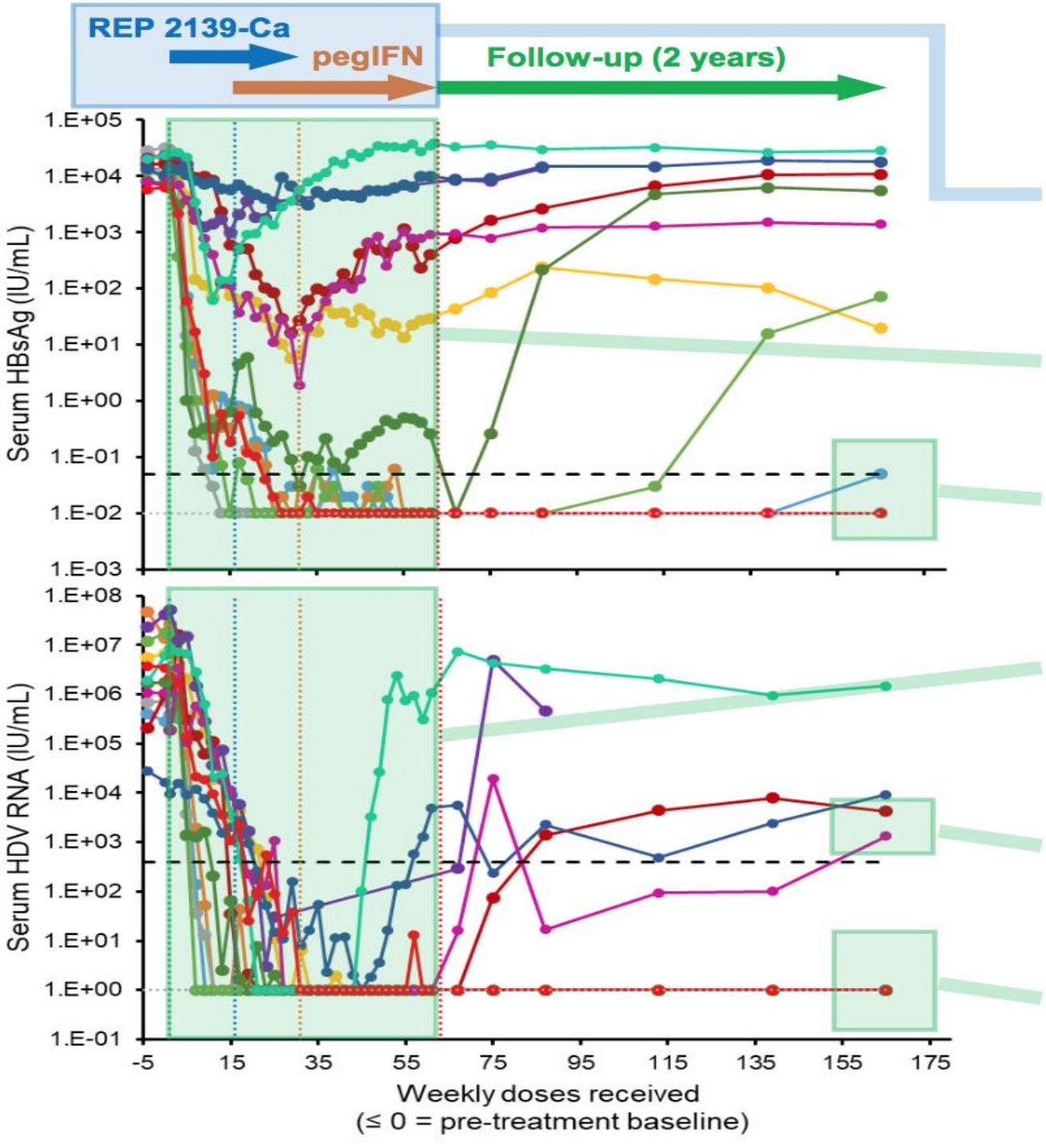
# Biochemical Response (ALT)

## Median ALT levels




## ALT normalization at week 48




REP 2139-Ca
pegIFN
Follow-up (2 years)
Serum HBsAg (IU/mL)
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
1.E-01
1.E-02
1.E-03
Serum HDV RNA (IU/mL)
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
1.E-01
-5
15
35
55
75
95
115
135
155
175
Weekly doses received
(≤ 0 = pre-treatment baseline)