# The role of NAPs in therapy of Chronic HDV infection

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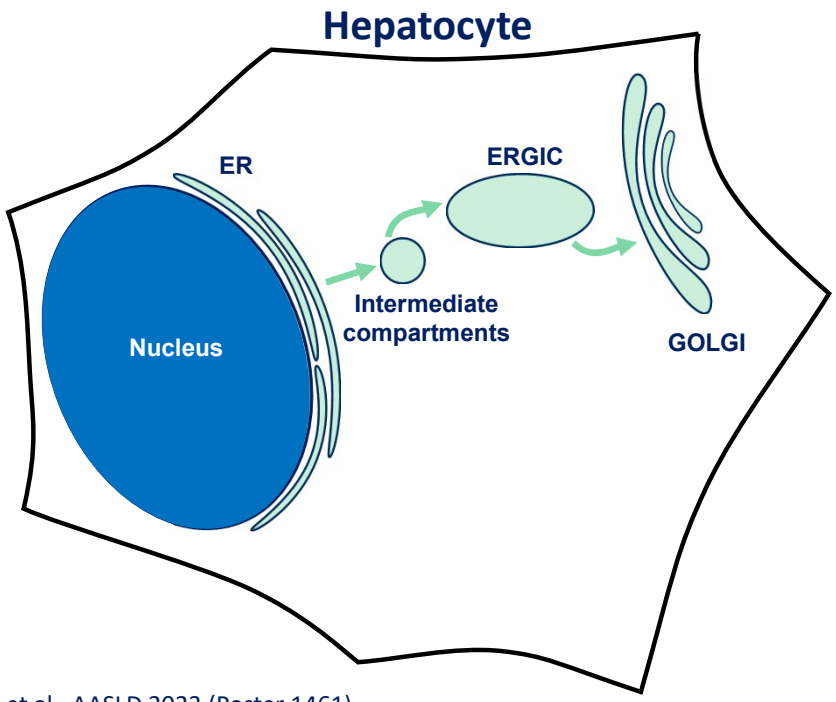
SCIENCE OF HBV CURE

# Conflict of interest

Employee / shareholder, Replicor Inc.

# Understanding how NAPs work in HBV / HDV co-infection




## Passage through secretory pathway (transient)

- Activity occurs at acidic pH (post ER)
- Targets the host HSP40 chaperone DNAJB12
- Blocks inhibition of HBV SVP assembly
- Blocks envelopment of HDV RNP

## Accumulation in nucleus

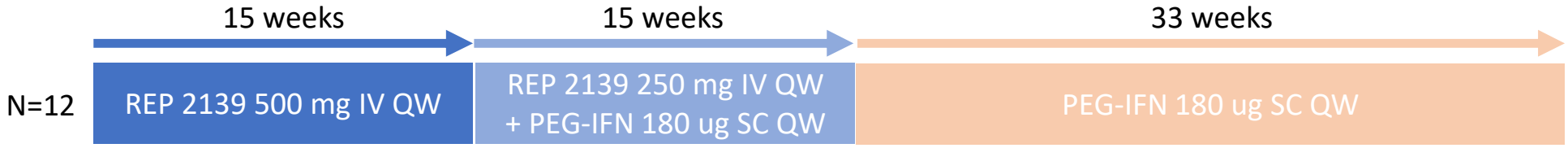
- Targets S-HDAg and L-HDAg
- Inhibits replication / morphogenesis of HDV upstream of RNA envelopment (mechanism under exploration)
- Nuclear accumulation is more efficient
- Anti-HDV effects are easier to achieve


Fonte et al., AASLD 2023 (Poster 1461)
Boulon et al AASLD 2020 (Poster LP-42)
Boulon et al., Antiviral Res. 2020; 183: 104853
Blanchet et al., J Virol. 2019; 164: 97-105
Bazinet et al., Lancet Gastro. Hepatol. 2017; 2: 877-889
Shamur et al., Hepatol. 2017; 66: 504A

# REP 2139 in HDV patients: phase II clinical trial data

Study REP 301: HDV patients, non-cirrhotics, HBeAg negative

**Suboptimal treatment regimen (first exposure in Caucasian patients)**




| | REP 2139 monotherapy | End of combination therapy | End of treatment |
|---|---|---|---|
| HBsAg reduction (log from baseline) | 3·31 (1·99) | 4·15 (2·24) | 3·45 (2·70) |
| HBsAg negative* | 2 (17%) | 4 (33%) | 5 (42%) |
| Anti-HBs positive† | 5 (42%) | 6 (50%) | 6 (50%) |
| HDV RNA reduction (log from baseline) | 4·21 (1·99) | 5·68 (1·14) | 5·34 (2·34) |
| HDV RNA negative‡ | 4 (33%) | 10 (83%) | 9 (75%) |

**7.4 years of follow-up (no antiviral therapy)**

- 64% (7/11) HDV RNA undetectable
- 4 (36%) with HBsAg loss (HBV functional cure)

Bazinet *et al*. Lancet Gastroenterol Hepatol 2017

# Replicor compassionate access program

- Compassionate access to REP 2139-Mg (RCAP, NCT05683548) in eligible patients:
  - Previous virologic or biochemical failure or rebound during therapy with pegIFN and/or bulevirtide
  - Patients with HBV / HDV decompensated cirrhosis
  - **Utilizes remaining drug supply from REP 401 trial (IV infusion)**

    Administration switched to bolus SC injection of 250mg

    Recall: similar liver accumulation observed for NAPs with IV or SC administration

- Patients enrolled worldwide:
  - France (18 patients, 8 centers)
  - Israel (1 patient, 1 center)
  - Austria (3 patients, 1 center)
  - Turkey (4 patients, 1 center)
  - Germany (1 patient, 1 center)
  - Italy (4 patients, 1 center)
  - Australia (1 patient, 1 center)
  - Canada (1 patient, 1 center)

# Patients and methods

- Patients received the following treatment for a planned duration of 48 weeks:
  - **REP 2139-Mg 250 mg QW SC (n=33)**
  - **TDF 245 mg QD PO (n=28) or TAF QD PO (n=5)**
  - **PegIFN 45-180ug qW SC if compensated disease and no contra-indication (n=18)**
- Safety and liver function were monitored weekly and antiviral response every 4 weeks with standard assays for quantitative HBsAg and anti-HBs, HBV DNA, HDV RNA and HIV RNA (in 2 HIV co-infected patients).

# RCAP baseline characteristics

| | N = 33 |
|---|---|
| Age (years)[#] | 47 (21 – 69) |
| Male Sex (n, %) | 21 (64 %) |
| Ethnicity | 24 Caucasian, 5 African, 2 Middle Eastern, 1 Asian, 1 Central Asian |
| Previous failure to pegIFN (n, %) | 24 (73 %) |
| Previous BLV treatment (n, %) | 20 (61 %) |
| Liver fibrosis (n)<br>Advanced fibrosis F3<br>Compensated cirrhosis<br>Decompensated cirrhosis | <br>5<br>22<br>6 |
| Positive HBeAg at baseline (n) | 6 |
| HDV genotype (n)<br>GT1 / GT5 / GT7 / Unknown | <br>19 / 4 / 1 / 9 |
| HIV co-infection (n) | 2 |
| HDV RNA (IU/mL) [#] | 1.96 x$10^6$ (295-1.68x$10^7$) |
| HBsAg (IU/mL) [#] | 8307 (626-33559) |
| HBV DNA (IU/mL) [#] | 1234 (TND-3440) |
| ALT (U/L) [#] | 88 (19-266) |
| Bilirubin (µmol/L) [#] | 17 (3.4-34) |

[#] Mean (range)

**BLV failure**

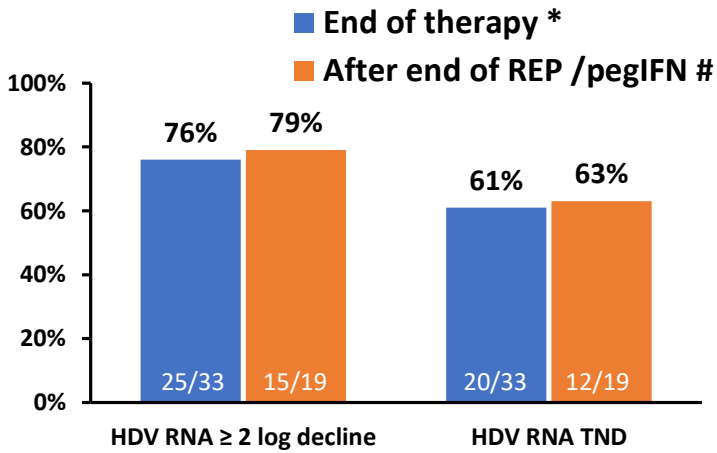
**9 poor response (< 2 $log_{10}$ in HDV RNA) during therapy**

**11 HDV RNA rebound during therapy**

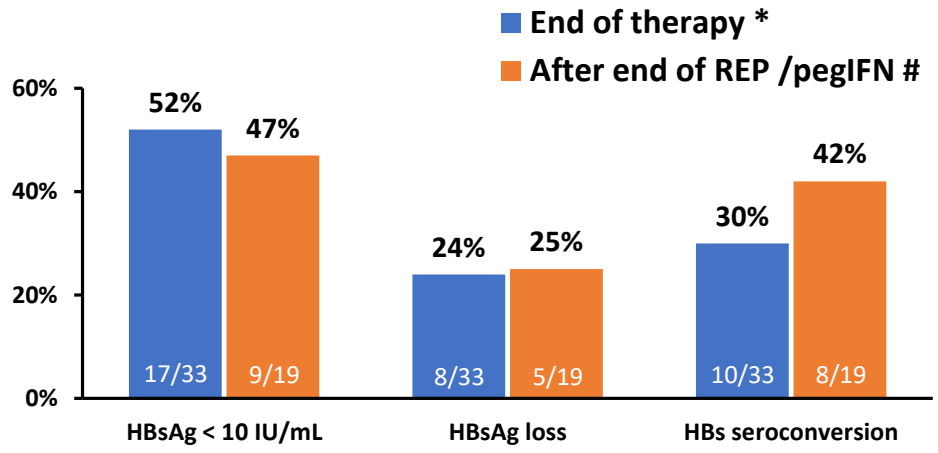
# Virological results on therapy and after REP 2139 treatment

## Interim results *#

### HDV RNA response




### HBsAg response




**ALT normalized in 47% (9/19) after end of REP / pegIFN**

**Removal of all antiviral therapy in three patients:**

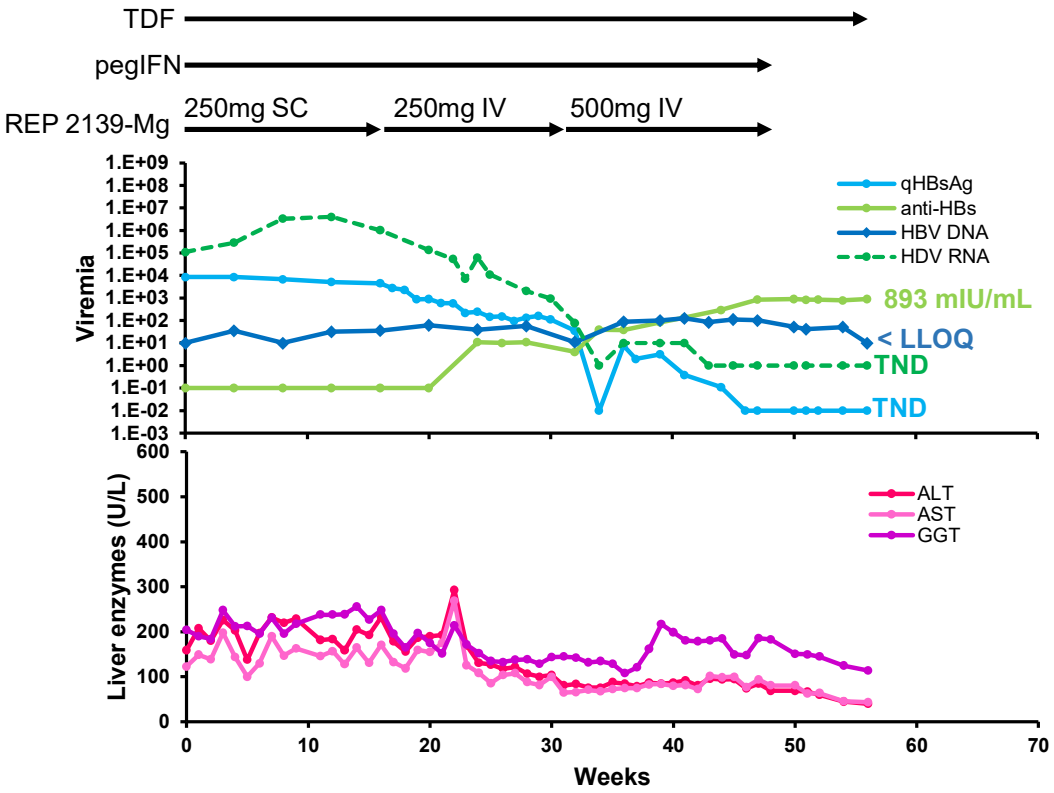
**all with HDV TND / HDV cure and HBV functional cure (24 weeks of follow-up)**

* 3 patients still on therapy: 1 has < 16 weeks, 2 on extension therapy > 48 weeks. 7 patients halted therapy prior to 48 wks; 2 due to LT, 2 due to poor IV access, 1 due to unrelated burst varices, 1 for futility and 1 due to lost contact.

# With available follow-up (4-48 weeks) after completion of at least 48 weeks of therapy. Four patients completed extension therapy totalling 60-80 weeks.

# Suboptimal virological response can be improved with REP 2139 dose modification and/or therapy extension

**RCAP #31: Christoph Neumann-Haefelin, Germany**

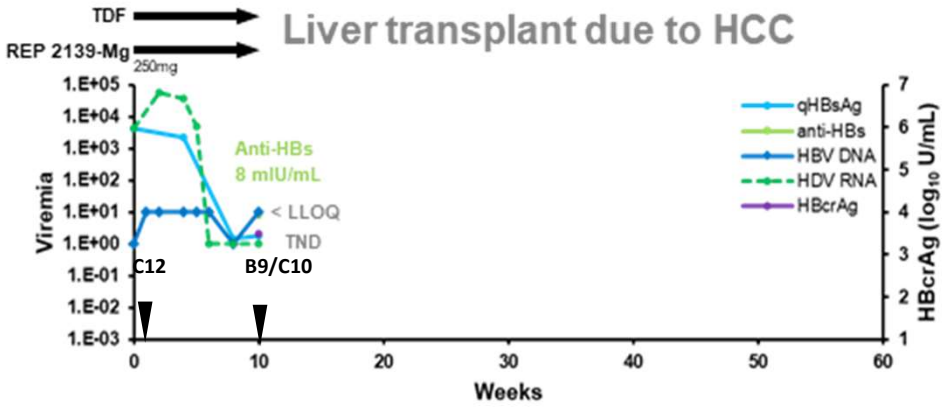



- 47 year old, Asian male, compensated cirrhosis with previous failure on pegIFN + BLV
- Initial poor response to 250mg SC is effectively rescued by modifying dosing to increase $C_{max}$
- HDV-RNA TND at W43 and HBsAg loss at W46

**Patient maintains HDV RNA TND and HBsAg loss with seroconversion 8 weeks off therapy (TDF only)**

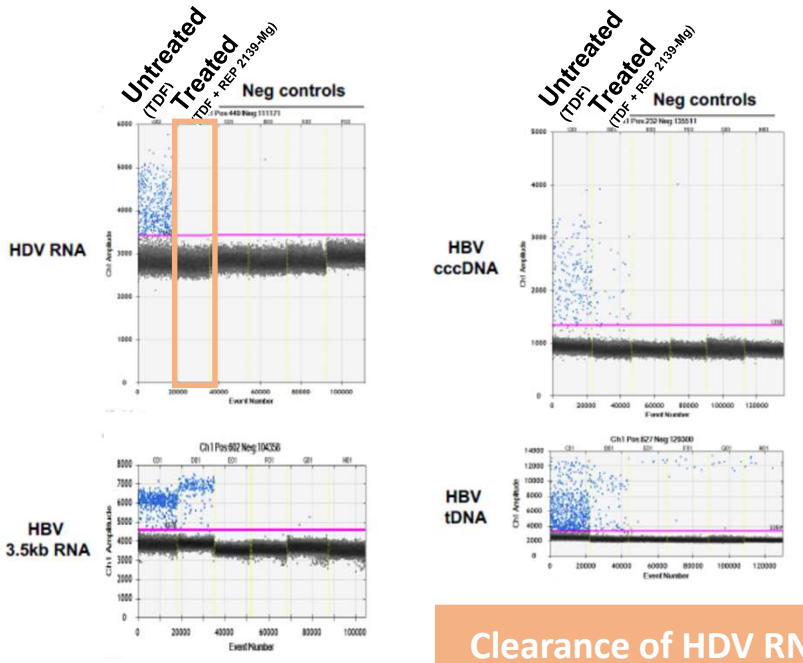
# Clearance of HDV RNA from the liver after 10 weeks of NAP therapy

**RCAP #8 Christiane Stern**
**56 years old, African female, GT5, HBeAg -**




- Significant reduction of ascites at week 4
- No progression of HCC, no ALT flare, no systemic AE
- **Transplant after 10 weeks of REP 2139**
- Explant has normal histology (non HCC regions)
  - No steatosis
  - Well differentiated HCC with no vascular emboli
  - **No ground glass hepatocytes**

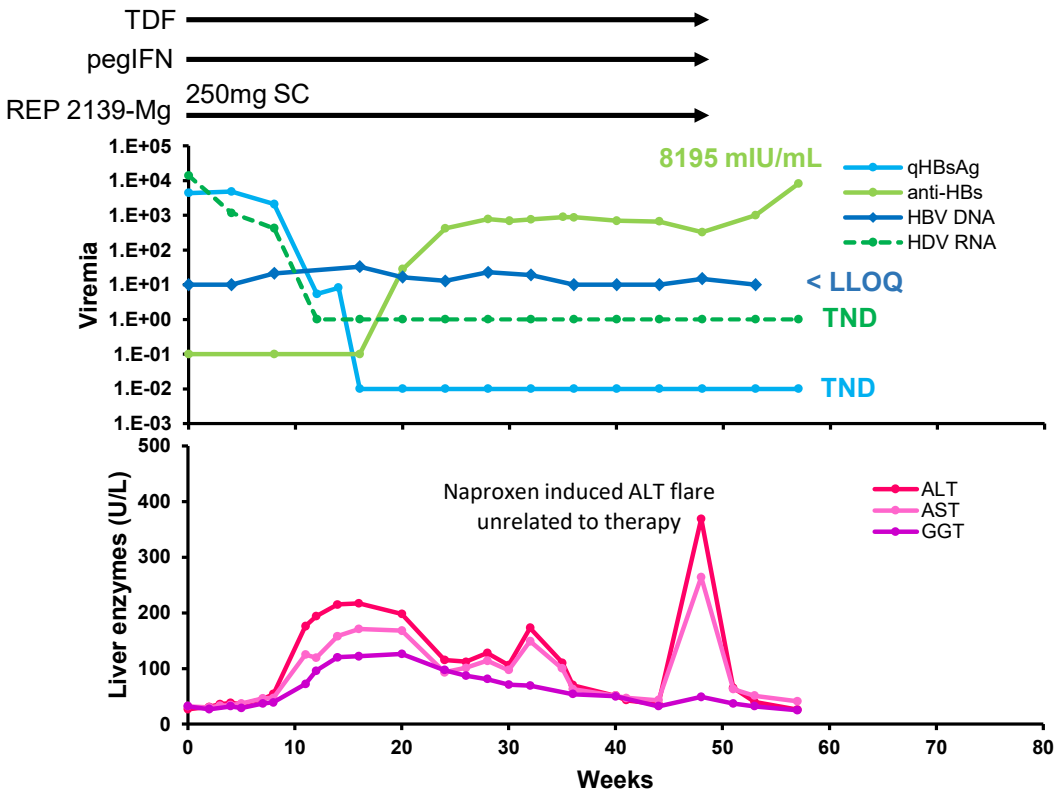
**Intrahepatic analysis of HDV and HBV markers in the liver explant**




**Clearance of HDV RNA from the liver explant with very low levels of cccDNA present**

# RCAP #15

## Cihan Yurdaydin, Istanbul, Turkey




53 year old Caucasian male
Compensated cirrhosis

Previous failure to pegIFN

**250mg SC can achieve HDV RNA and HBsAg loss and seroconversion**

**Establishes HDV cure and HBV functional cure in combination with pegIFN**

# RCAP #5

## Christiane Stern, Versailles, France

Caucasian female, 45 years old

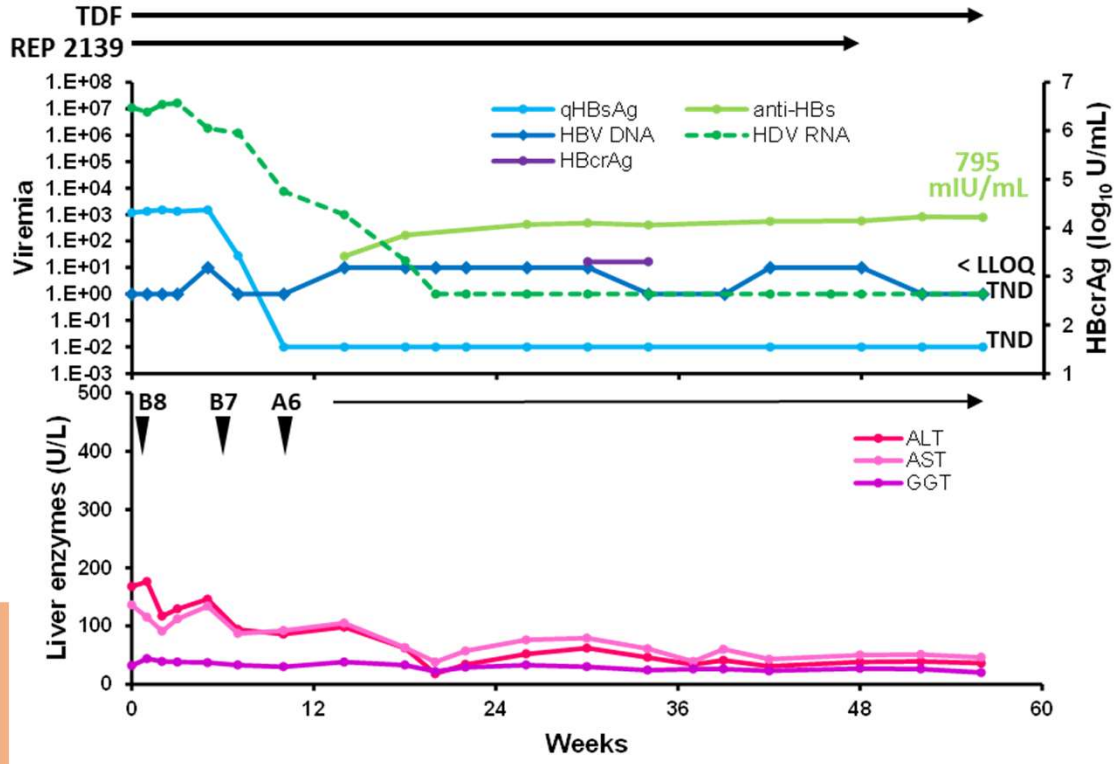
HDV GT-1, decompensated cirrhosis

Pronounced ascites – awaiting liver transplant
pegIFN and BLV contraindicated

**Rapid elimination of ascites at week 4**
**Recompensation of cirrhosis (Child B8 to A6)**
**No ALT flare, no systemic AE**

**Persistent HDV RNA and HBsAg loss 6 months following removal of REP 2139-Mg**

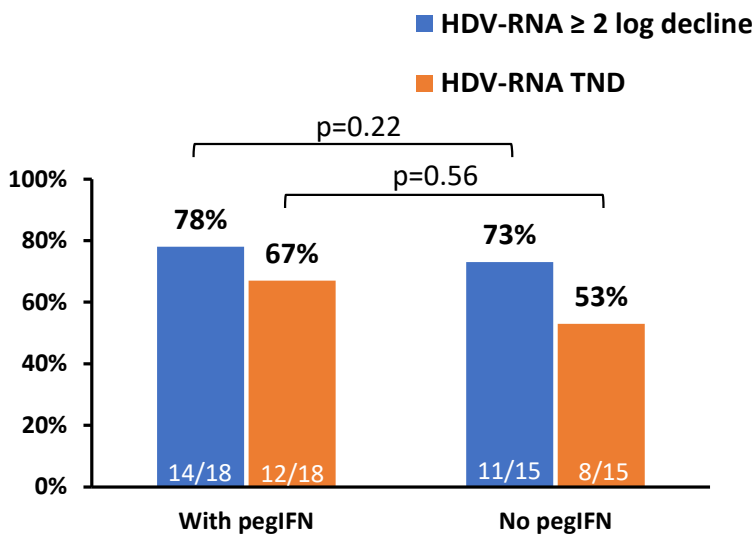
**Patient has been removed from the transplant list**



# No baseline predictive factors of virological response

| Baseline parameter | HDV RNA TND during therapy | HBsAg log reduction from baseline during therapy |
|---|---|---|
| Age | p=0.94[B] | p=0.87[A] |
| Sex | p=0.99[E] | p=0.62[B] |
| Ethnicity<br>Caucasian versus non-Caucasian | p=0.46[E] | p=0.36[B] |
| BMI | p=0.29[B,C] | p=0.25[A,C] |
| ALT | p=0.57[B] | p=0.63[A] |
| Liver disease<br>Compensated cirrhosis / fibrosis versus decompensated cirrhosis | p=0.06[E,F] | p=0.76[B] |
| HDV RNA | p=0.54[B] | p=0.79[A] |
| HBsAg | p=0.82[B] | p=0.99[A] |
| Absence of pegIFN during therapy | p=0.56[E] | p=0.25[B,D,G] |

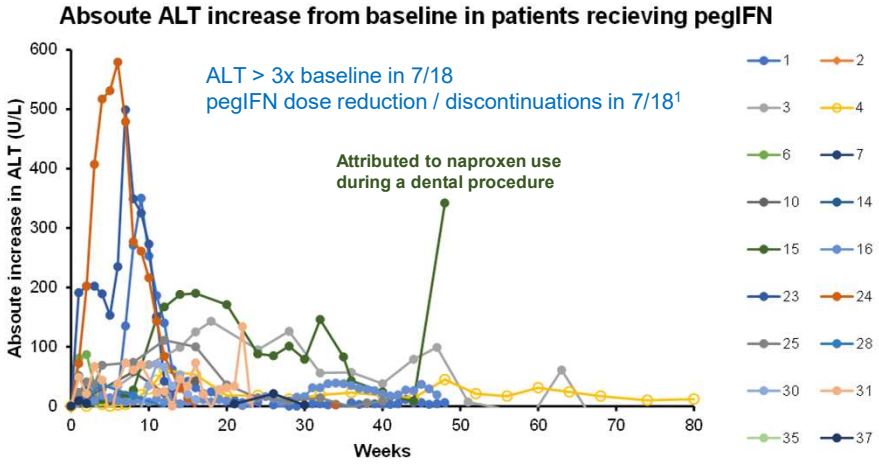
## Virological response according to pegIFN therapy

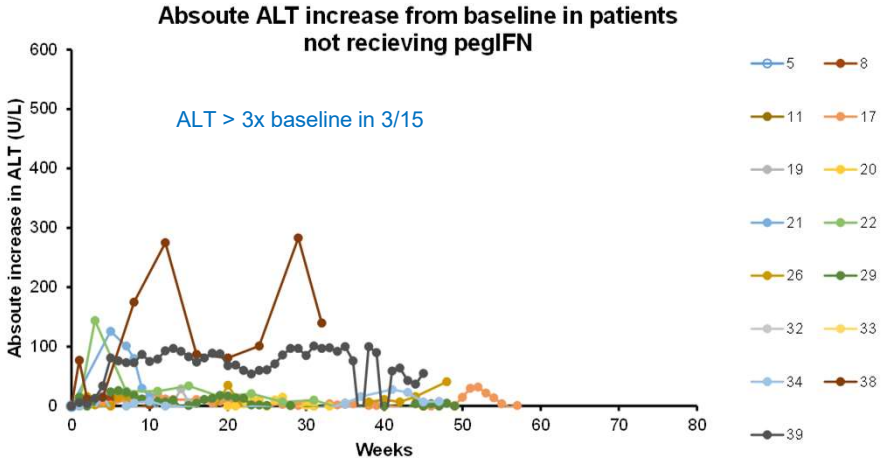



A. Regression analysis
B. T-test
C. Baseline BMI is not available for 10 patients
D. No significant differences in baseline HDV RNA (p=0.37) or HBsAg (p=0.88) were present between –pegIFN and +pegIFN groups.
E. $X^2$ analysis
F. May reflect bias due to small sample size (decompensated cirrhosis n=6) and 3/6 decomps halted therapy early (2 transplant, 1 burst varices not related to REP 2139-Mg exposure).
G. Change to lack of significance from original abstract submission is attributed to additional REP 2139-Mg dose escalation and or therapy extension since submission of abstract.

# REP 2139 is safe and well tolerated in HDV cirrhotics

- No SAE related to REP 2139-Mg
- Reported REP 2139-Mg AE: 1. transient mild injection site reactions (55%)
  2. grade 1-2 thrombocytopenia (18%) self resolving after removal of REP 2139-Mg
- ALT flares are asymptomatic and self resolving (mainly with pegIFN)
  - lower in intensity and prevalence than observed in prior clinical trials




1. one transient reduction (lip lesions), 1 discontinuation due to unavailability (switch in manufacturer) and 5 discontinuations due to AE (fatigue, anemia, petechial hemorrhages, hyperbilirubinemia[2])
2. in one patient with previous poor tolerability to pegIFN, pegIFN was halted to reverse hyperbilirubinemia, REP 2139-Mg dosing was not altered

# Summary

- REP 2139-Mg SC is well tolerated and safe in compensated and decompensated HDV cirrhosis
- ALT flares remain asymptomatic but are weaker and less frequent than in non-cirrhotic patients in previous trials
- HDV cure and HBV functional cure is possible in these difficult to treat patients, even in the absence of pegIFN
- **Suboptimal HDV RNA and HBsAg responses in patients are caused suboptimal hepatocyte loading of NAPs**
- In patients with suboptimal response to 250mg SC, increasing REP 2139 doses, transitioning to IV or therapy extension improved antiviral response
    - **Dose transitioning increases $C_{max}$ and improves hepatocyte uptake**
- A novel SC formulation of REP 2139-Mg is currently in development to improve $C_{max}$ in all patients
    - **Increased rates of HDV cure and HBV functional cure are expected**

# The RCAP investigators and supporting scientists

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