Safety and efficacy of REP 2139-Mg in hepatitis D patients: reporting of extended follow-up data from the international compassionate use program

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*On behalf of the RCAP investigators

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Conflict of interest

Consultant: EchoSens

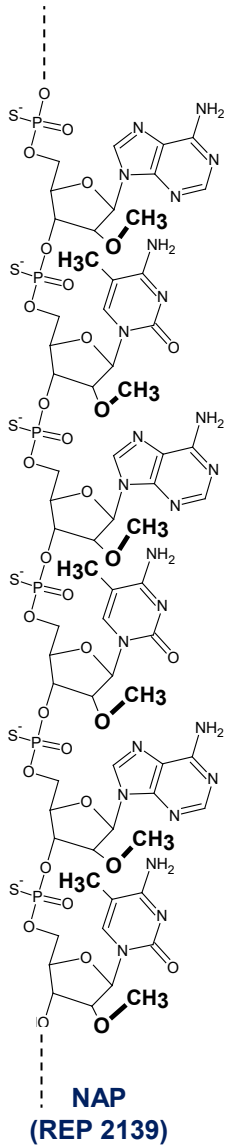
Speaker: Hologic, Gilead

Stock options: Gilead

Travel grants: Gilead, AbbVie, Grifols

Except for M. Bazinet and A. Vaillant, no authors have a conflict of interest with Replicor Inc.

REP 2139 in HDV patients: *in vitro* data



NAP
(REP 2139)

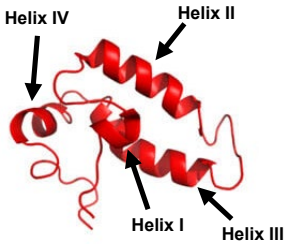
40mer oligonucleotide polymer of alternating adenosine and cytidine =

optimal target interaction, prevents host genome interactions and immunostimulation

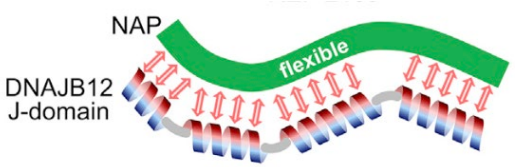
Mechanism of action

Passage through secretory pathway (transient)

- Target the host HSP40 chaperone DNAJB12
- Inhibition of HBV SVP assembly
- Blocks envelopment of HDV RNP



J-domain crystal structure of DNAJB12 at neutral pH
(4 linked alpha helices)



Flexible nature of NAPs adapts to minor alterations in α-helical confirmation, maintaining high affinity interactions

Accumulation in nucleus

- Targets S-HDAg and L-HDAg
- Inhibits HDV RNA replication
- Blocks HDV RNA interaction with HDAg during HDV RNP morphogenesis
- **Nuclear accumulation is more efficient**
- Anti-HDV effects are easier to achieve than for HBV

HDAg crystal structure

Vaillant A, ACS Inf Dis 2019. Vaillant A, Antiviral Res 2016. Levrero M *et al*, AASLD 2023.

REP 2139 in HBV and HDV: phase IIa clinical trial data

Study REP 401: HBV patients, non-cirrhotics, HBeAg negative

NAPs + TDF + pegIFN (48 weeks), 40 patients

Long-term follow-up of 5.3 years (no antiviral therapy present):

- Partial cure remains stable (78%)
- HBV functional cure rate increased from 39% at 1 year follow-up to 56% at last follow-up

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

REP 2139-Ca (30 weeks) + pegIFN (48 weeks with 15 weeks of NAP overlap), 12 patients

Long-term follow-up of 7.4 years (no antiviral therapy present), 11 patients:

- 91% remain off NUC therapy (normal ALT)
- 82% HDV RNA > 2 log decline with normal ALT
  - 64% HDV RNA undetectable
  - 64% with HBV partial cure (HBV DNA < 2000 IU/mL)
  - 36% with HBV functional cure (HBV DNA and HBsAg TND)

Bazinet M *et al,* Gastroenterology 2020. Vaillant *et al,* GHS 2023. Bazinet M *et al,* Lancet Gastroenterol Hepatol 2017. Vaillant *et al,* GHS 2023.

Replicor compassionate access program

- Compassionate access to REP 2139-Mg (RCAP, NCT05683548) in eligible patients:
  - Patients with HBV / HDV decompensated cirrhosis
  - Previous virologic or biochemical failure or rebound during therapy with pegIFN and/or bulevirtide
  - Utilizes remaining drug supply from REP 401 trial, but transitioning to weekly SC administration of 250mg as same organ 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)

Objective

- To evaluate the real-life safety and efficacy of REP 2139 in HDV patients with advanced liver disease in an international compassionate access program (RCAP, NCT05683548)

Patients and methods

- All 33 HDV patients enrolled in the compassionate access program were included
- 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

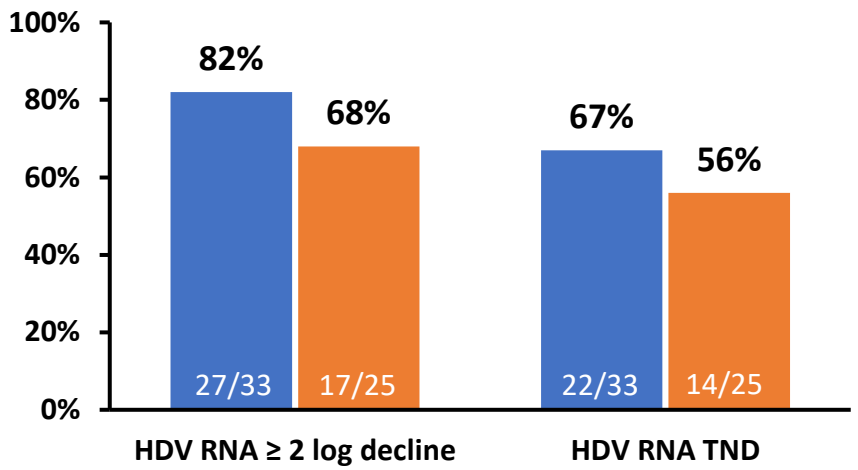
	N = 33
Age (years)#	47 (21 – 69)
Male Sex (n, %)	21 (64 %)
Ethnicity	24 Caucasian, 5 African, 2 Middle Eastern, 1 Asian, 1 Central Asian
Previous failure to pegIFN (n, %)	24 (73 %)
Previous BLV treatment (n, %) *	20 (61 %)
Liver fibrosis (n) Advanced fibrosis F3 Compensated cirrhosis Decompensated cirrhosis	 5 22 6
Positive HBeAg at baseline (n)	6
HDV genotype (n) GT1 / GT5 / GT7 / Unknown	 19 / 4 / 1 / 9
HIV co-infection (n)	2
HDV RNA (IU/mL) #	1.96 x10^6 (295-1.68x10^7)
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)

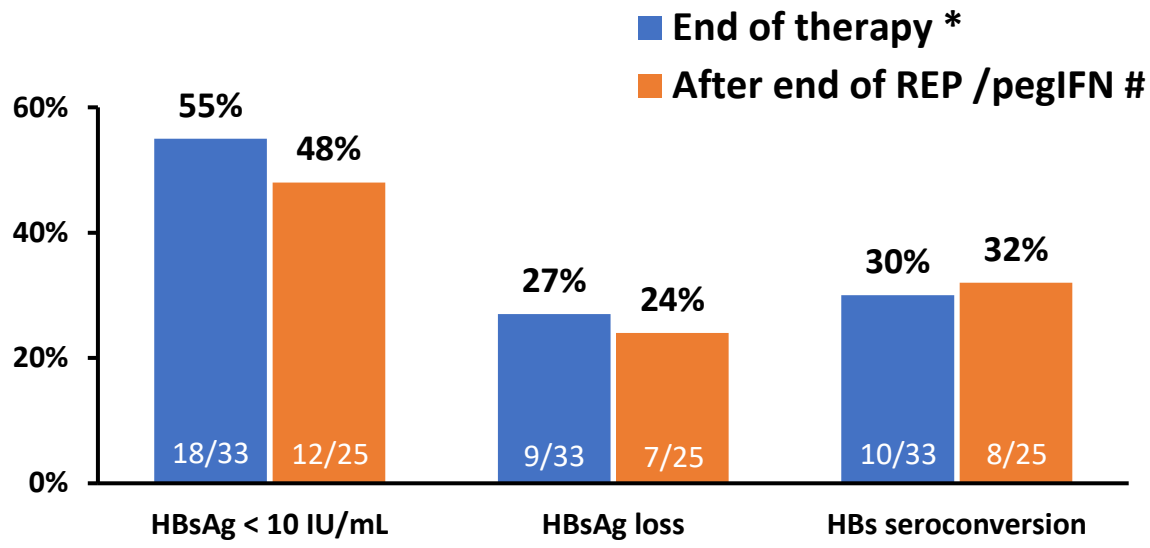
*9 non response (< 2 $\log_{10}$ in HDV RNA) and 11 HDV RNA rebound during therapy

Virological results on therapy and after REP 2139 treatment

HDV RNA response



HBsAg response



Poor initial antiviral response‡ was rescued with 250mg IV or 500mg (SC or IV) and/or treatment extension in 86% (18/21) patients

Removal of all therapy in 4 patients: all with HDV RNA TND and HBV functional cure (4§, 26, 32§ and 60§ weeks follow-up)

§ 64, 48 and 33 wks TDF monotherapy lead out respectively

Normal ALT in 52% (13/25) after end of REP / pegIFN

* 1 patient still on therapy (extension); 6 patients halted therapy prior to 48 wks; liver transplant (n=2), lost to follow-up (n=1), variceal bleeding (n=1) and problematic IV access (n=2). 6 patients completed extension therapy totalling 60-80 weeks

\# With available follow-up (8-93 weeks, median 24 weeks) after removal of REP 2139-Mg / pegIFN following completion of ≥48 weeks therapy

‡ <2 log decline in HDV RNA and/or <1 log decline in HBsAg

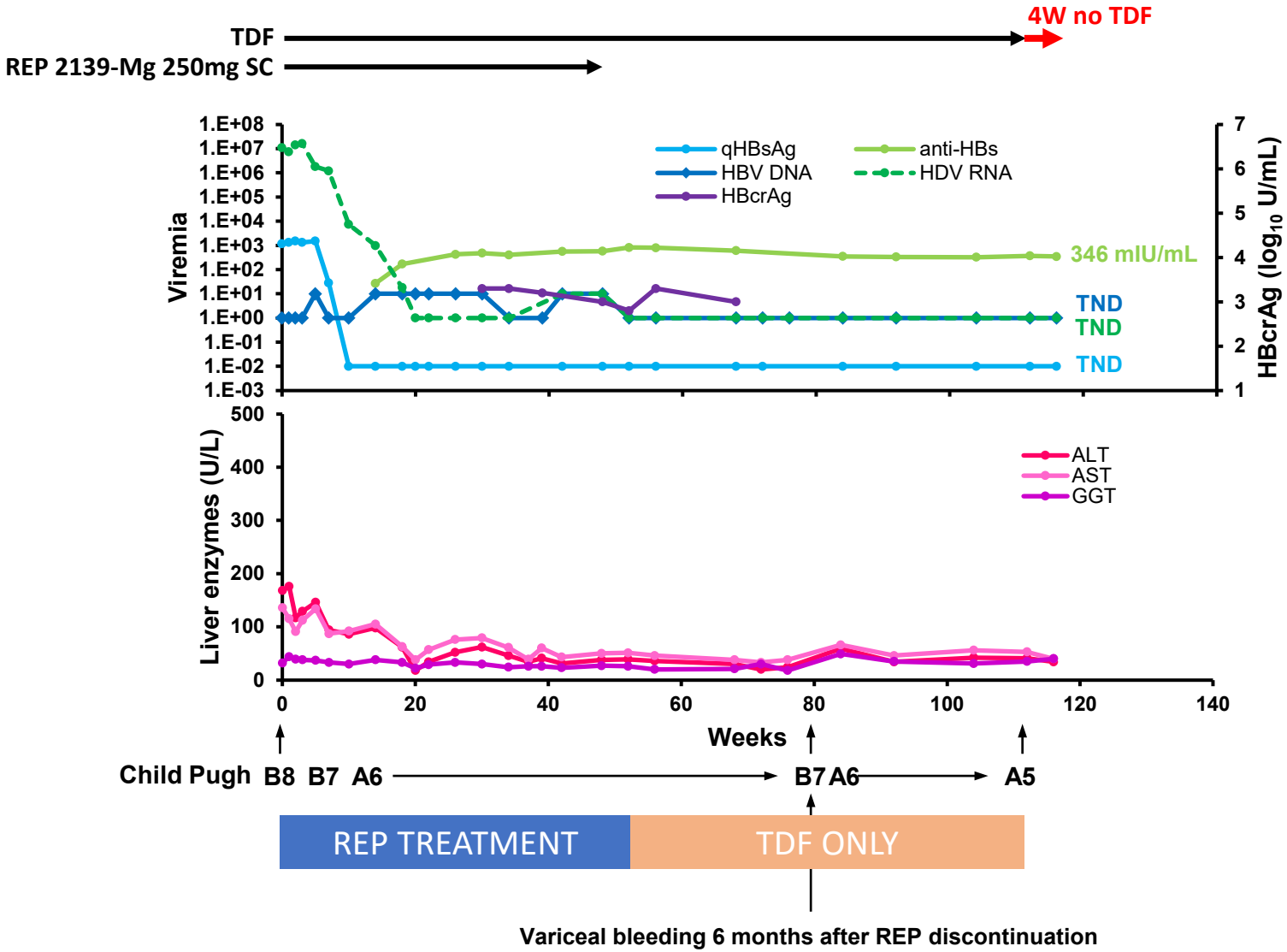
Liver function improvement with HDV cure and HBV functional cure in the absence of pegIFN

- 54 yo, Caucasian female, treatment naïve, decompensated cirrhosis (Child B8)
- HBsAg TND at W10
- anti-HBs seroconversion at W14
- HDV-RNA TND at W20

Ascites reversal since W4

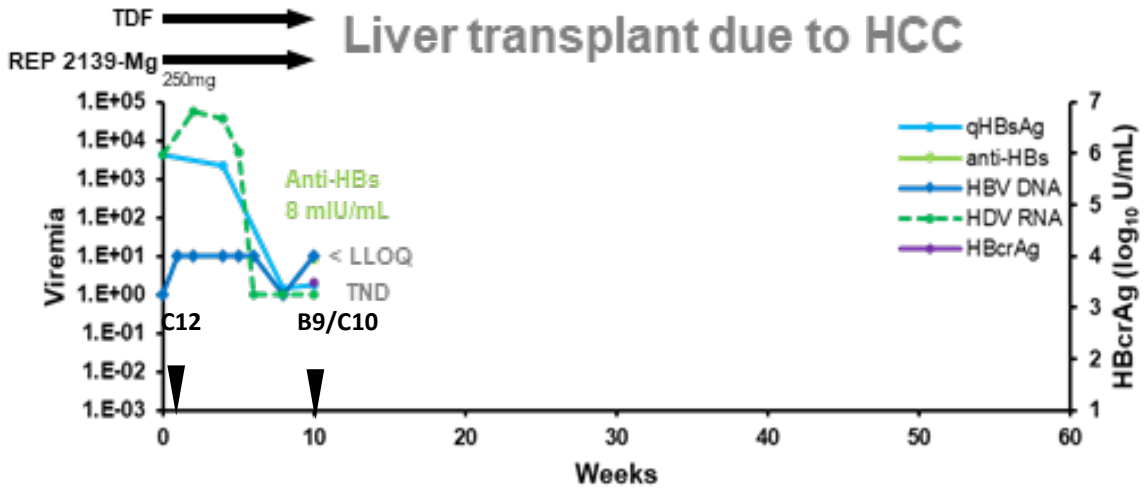
Compensated cirrhosis at W10

4 weeks off all therapy (TDF removed): HDV RNA, HBV DNA and HBsAg TND



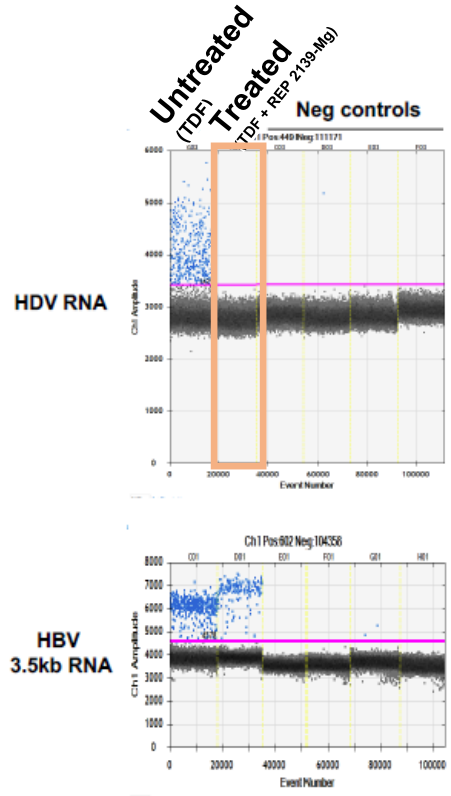
Clearance of HDV RNA from the liver after 10 wks of REP therapy

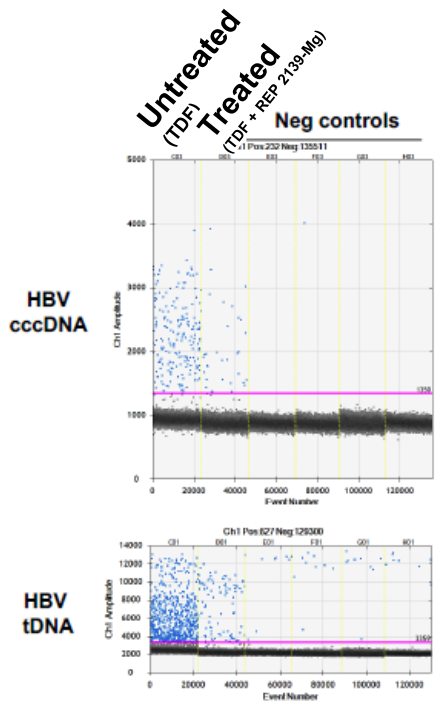
56 years old, African female, GT5, HBeAg -



- 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





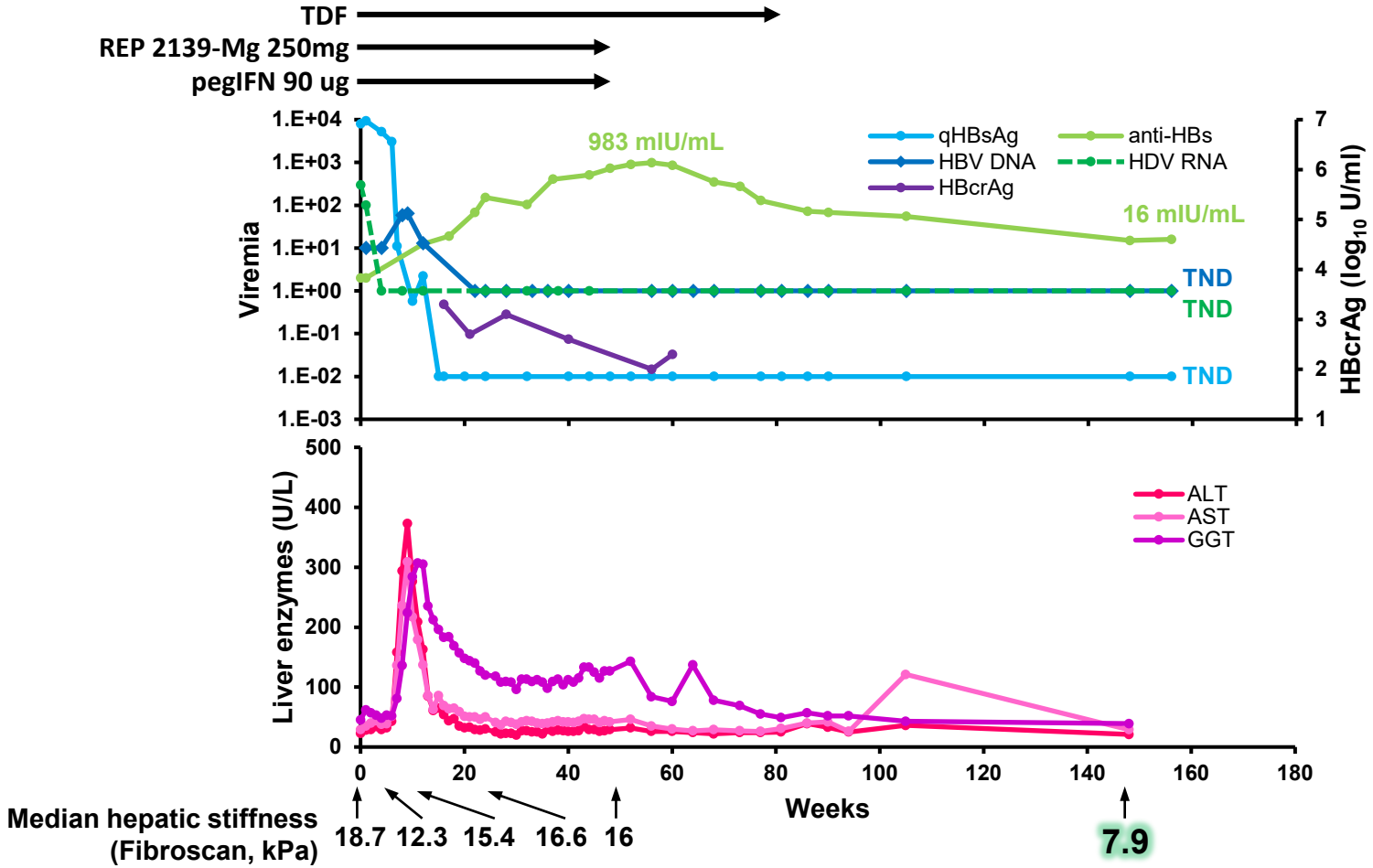
Clearance of HDV RNA from the liver explant with very low levels of cccDNA present

In collaboration with Barbara Testoni, France.

Reduction of liver elastography in a cirrhotic patient following achievement of HDV cure and HBV functional cure

- 51 year old, African male
- Previous treatment failure:
  TDF + pegIFN
  TDF + pegIFN + 2mg BLV
- HDV-RNA TND at W4
- HBsAg TND at W16
- anti-HBs seroconversion at W12

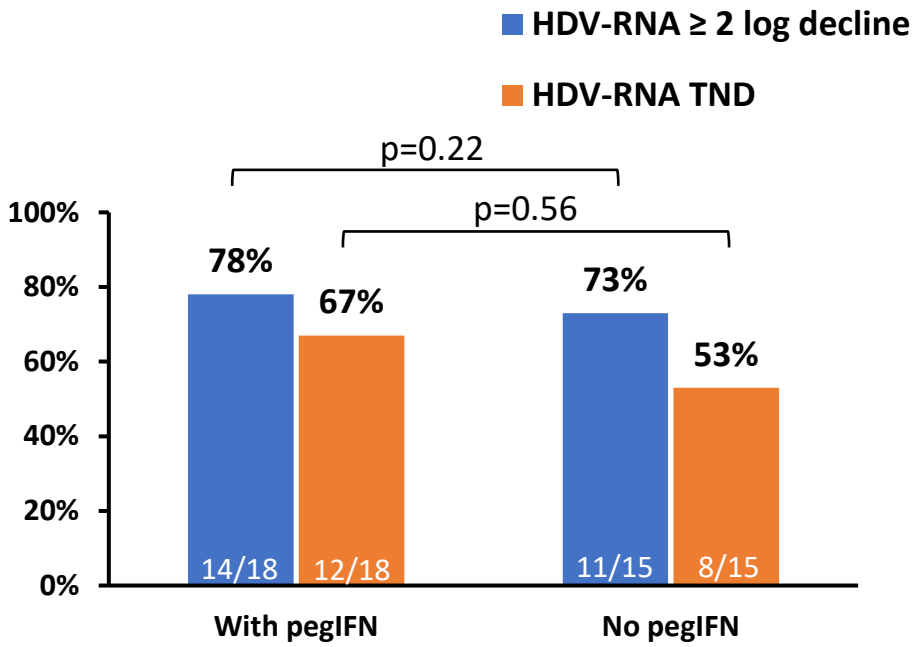
58% reduction in liver stiffness measurement with extended follow-up



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 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 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]

On therapy virological response according to pegIFN therapy

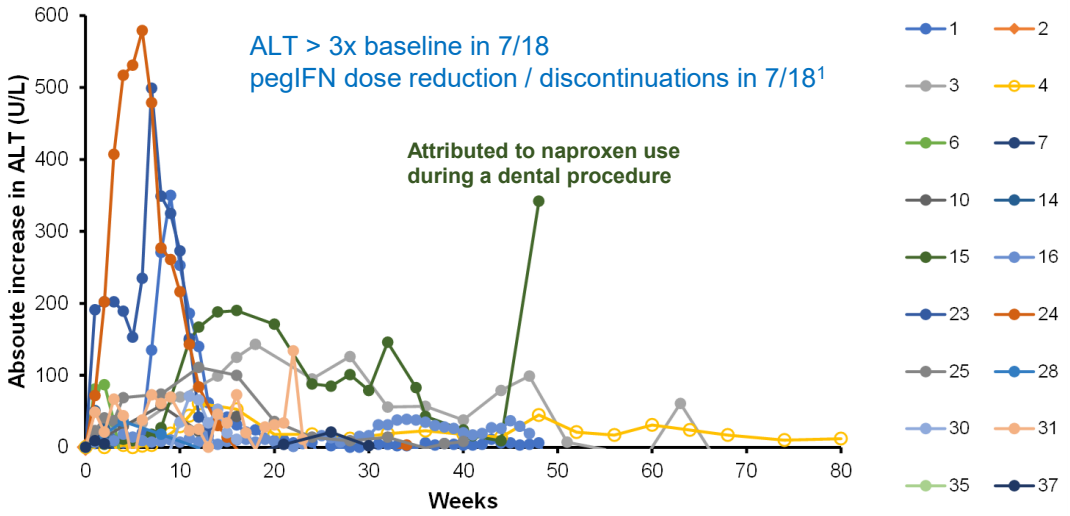


A. Regression analysis
B. T-test
C. Baseline BMI is not available for 10 patients
D. No significant differences in baseline HDV RNA (p=0.37) or HBsAg (p=0.88) were present between –pegIFN and +pegIFN groups.
E. X^2 analysis
F. May reflect bias due to small sample size (decompensated cirrhosis n=6) and 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.

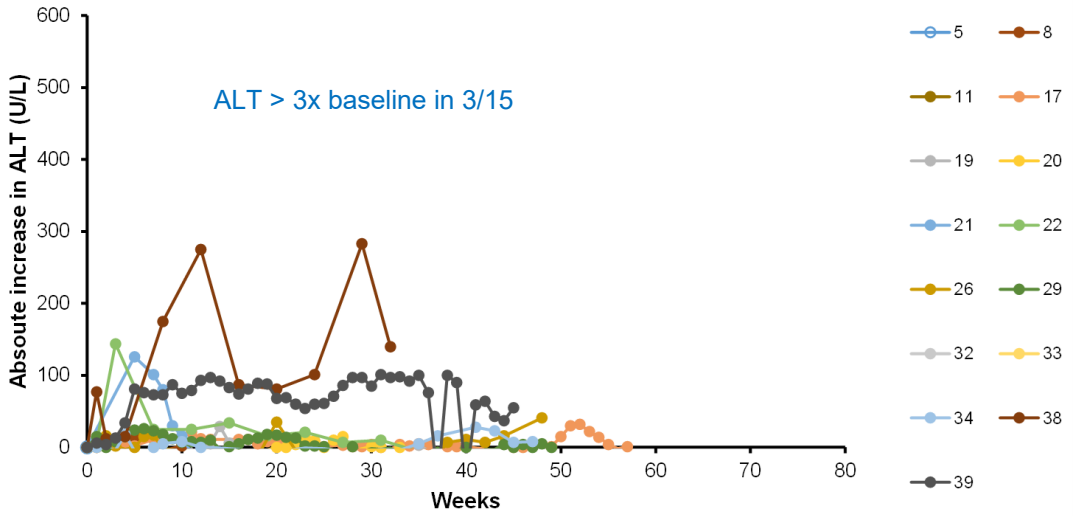
REP 2139 is safe and well tolerated in HDV cirrhotics

- 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)
  - Appear to be lower in intensity and prevalence than observed in prior NAP clinical trials in non cirrhotic patients

Absolute ALT increase from baseline in patients receiving pegIFN



Absolute ALT increase from baseline in patients not receiving pegIFN



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
- HDV cure and HBV functional cure is possible in these difficult to treat patients, even in the absence of pegIFN
- Improvement of liver stiffness in advanced liver disease may be possible during the follow-up period after REP 2139 treatment
- ALT flares are asymptomatic and appear to be less intense and prevalent than in previous NAP trials with non-cirrhotic patients
- A novel SC formulation of REP 2139-Mg is currently in development to increase hepatocyte uptake and improve antiviral responses against HBV and HDV

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