Rescue of cirrhotic HBV / HDV infection from bulevirtide failure by subcutaneous REP 2139-Mg

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Nucleic acid polymers (NAPs) in viral hepatitis

Lead NAP is REP 2139 (REP 2139-Mg formulation prevents injection site reactions)

Blocks assembly of HBV subviral particles (SVP) from cccDNA and integrated HBV DNA

- **Unique effect amongst antivirals in development**
- Host target: DNAJB12, a novel HSP40 chaperone critical for SVP assembly
- Rapid HBsAg loss (up to 7 $\log_{10}$ decline from baseline), regardless of baseline HBsAg or genotype
- Combined with pegIFN in HBV monoinfection:

  78% of patients maintain immune control / normal liver function off therapy

  39% with functional cure

Binds to the small and large forms of hepatitis delta antigen (HDAg)

- Achieves HDV RNA loss in 100% of patients to date
- Combined with pegIFN in a suboptimal regimen in HBV / HDV co-infection:

  64% of patients with undetectable HDV DNA and normal liver function off therapy

  All with functional or partial cure of HBV

Shamur et al., Hepatol. 2017; 66: 504A
Bazinet et al., Lancet Gastroenterol Hepatol 2017; 2: 877-889
Bazinet et al., Hepatology Comm. 2020 5: 189-202
Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Boulon et al., Hepatol. 2021; 74: 512A
Bazinet et al., J Viral Hep 2021; 28: 817-825
Bazinet et al., Hepatol Comm 2021; 28: 817-825

The burden of HBV / HDV co-infection

HDV is a obligate satellite infection of HBV

HDV replication uses the HBV subviral particle assembly pathway for envelopment

70% progression to cirrhosis within 10 years

15-40 million patients are affected worldwide

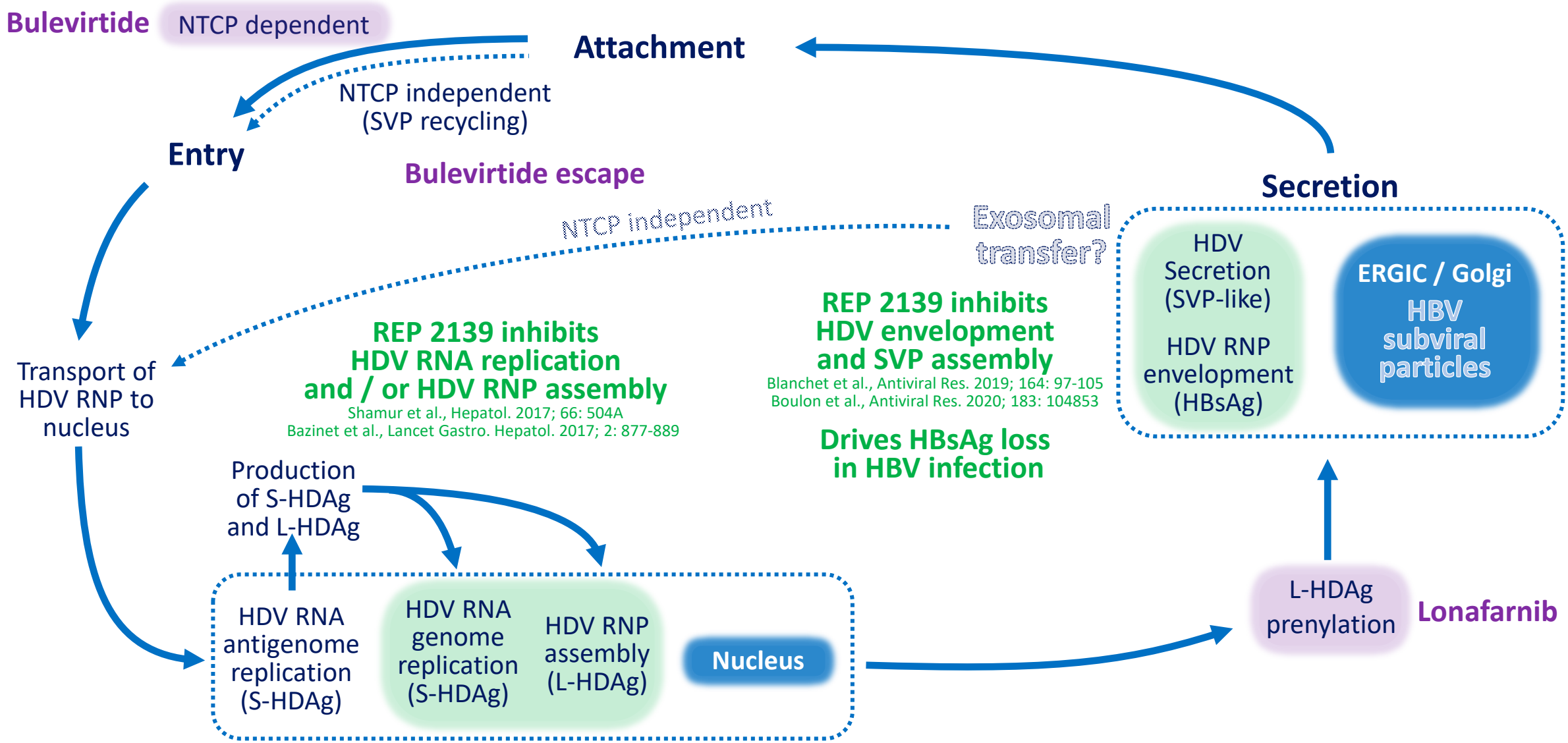
Approved agents: bulevirtide (blocks NTCP-independent HDV entry)

2mg monotherapy: ≥ 2$\log_{10}$ decline in HDV RNA in 71%
HDV RNA loss 12%
ALT normalization in 51%

non-response or viral rebound occurs in a significant minority of patients

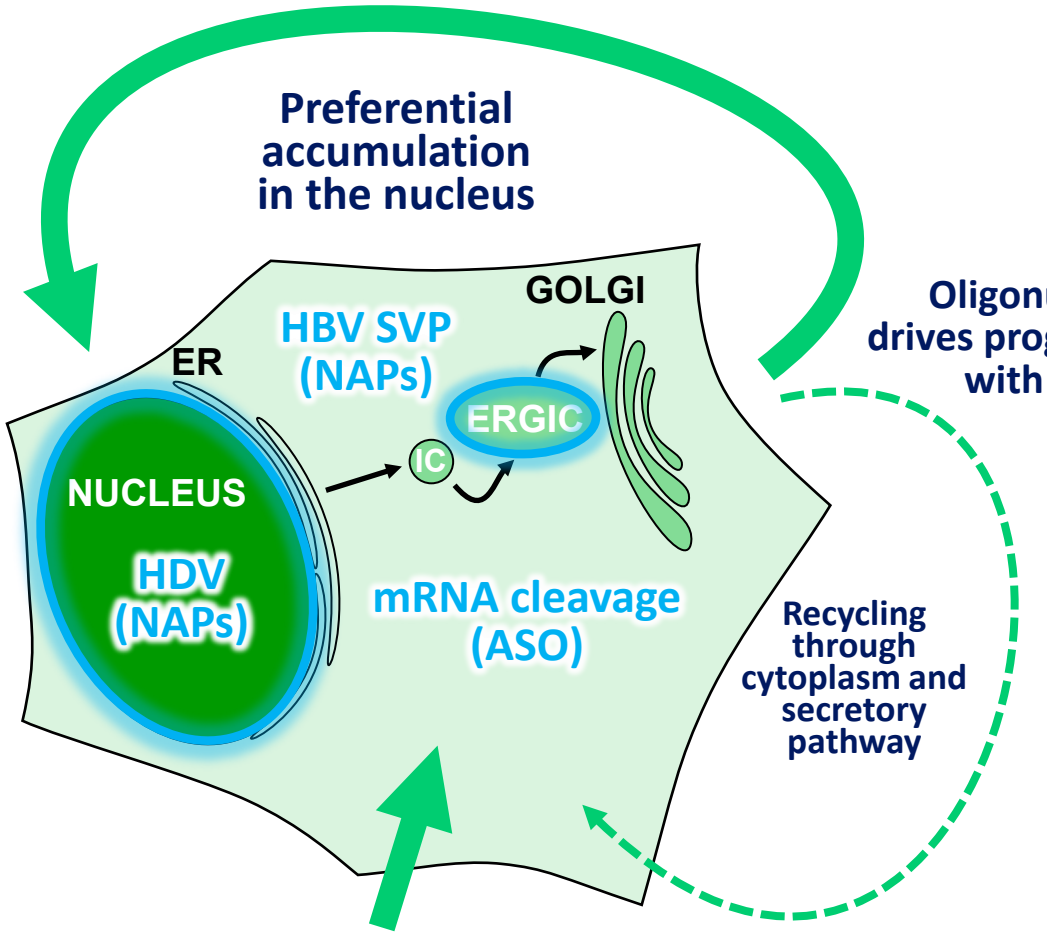
Wedemeyer et al., J Hepatol 2022; 77: S4

Targeting HDV replication with REP 2139



Intracellular accumulation of REP 2139 drives antiviral activity

Occurs with NAPs and ASOs



Oligonucleotide recycling drives progressive accumulation with repeated dosing

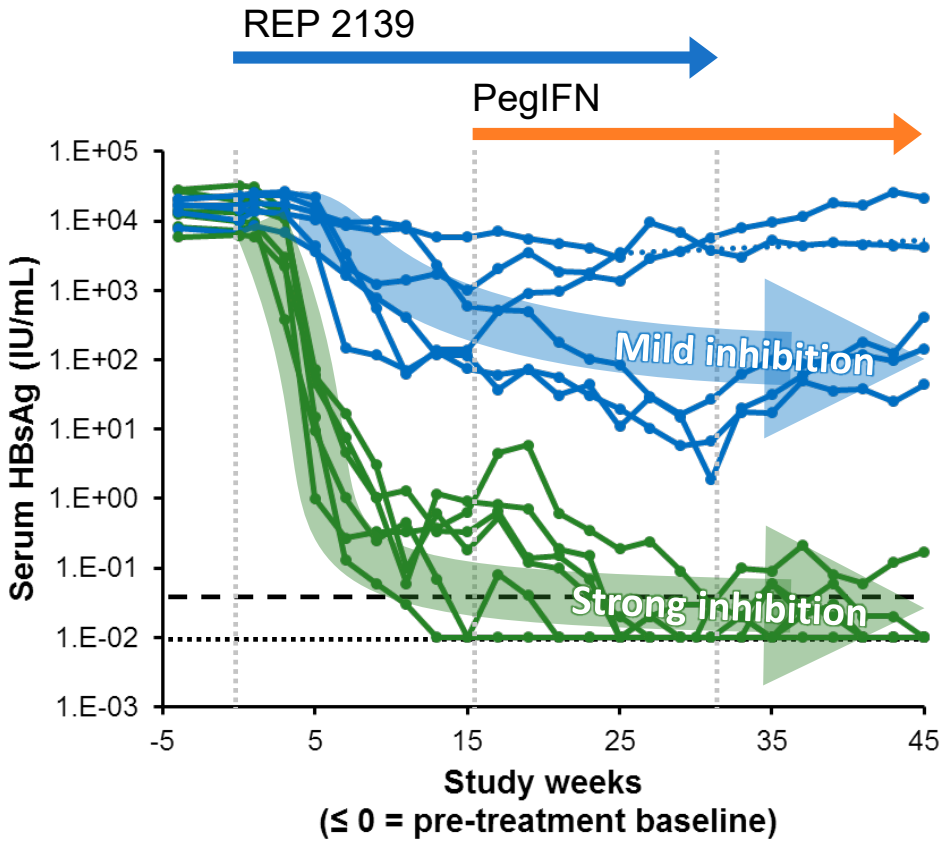
Transient passage through cytoplasm and secretory pathway

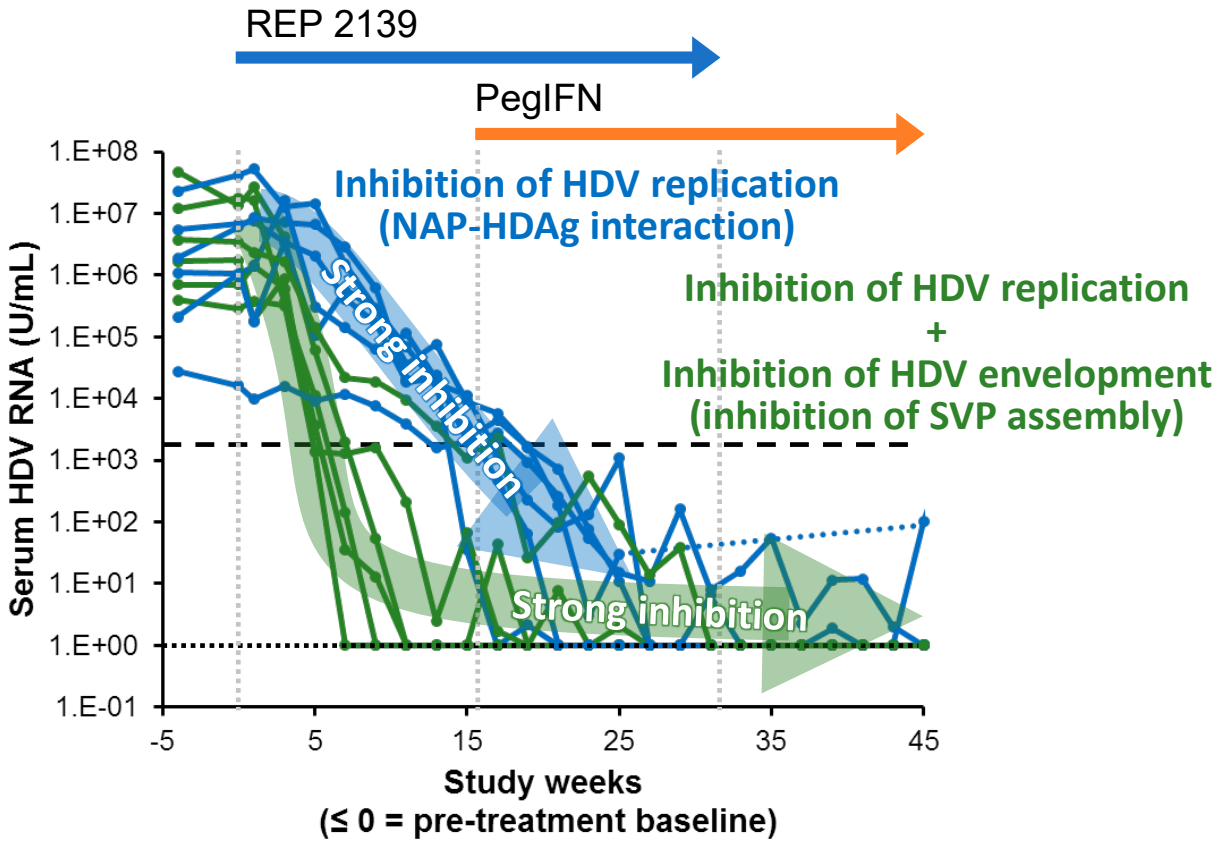
Minimal accumulation

HDV RNA response to REP 2139 is typically faster than HBsAg

Previous HDV efficacy (REP 301 study)

Strong HDV RNA declines with REP 2139 occur even when inhibition of SVP assembly is attenuated

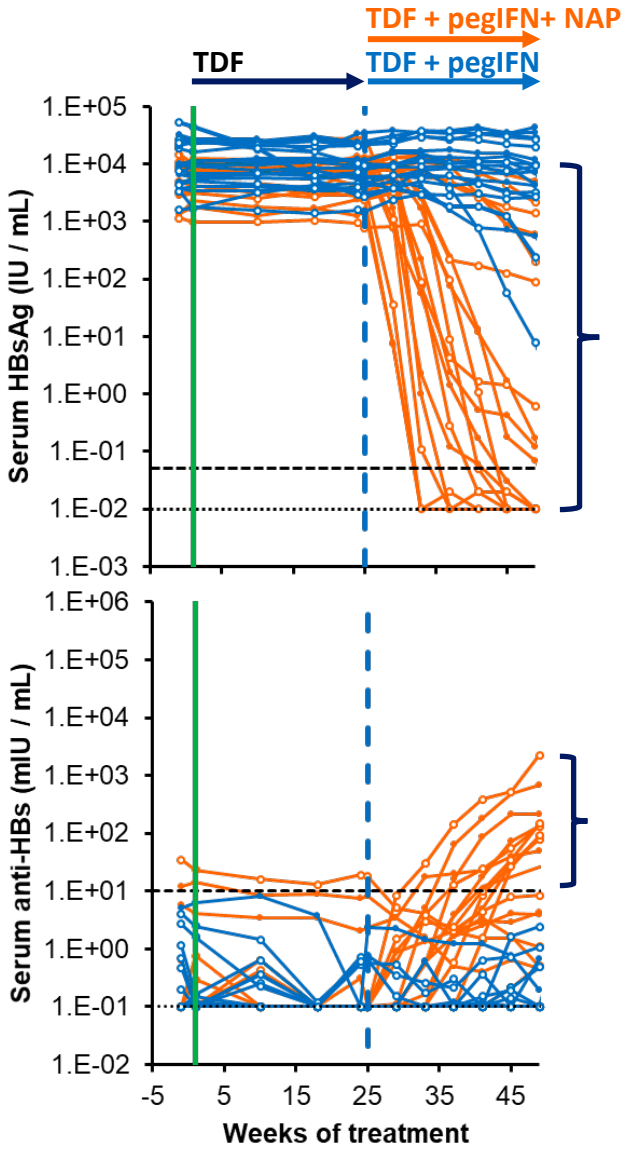




Functional cure of HDV (HDV TND, normal ALT)
in 64% patients after 3.5 years of no therapy
(all with partial or functional HBV cure)

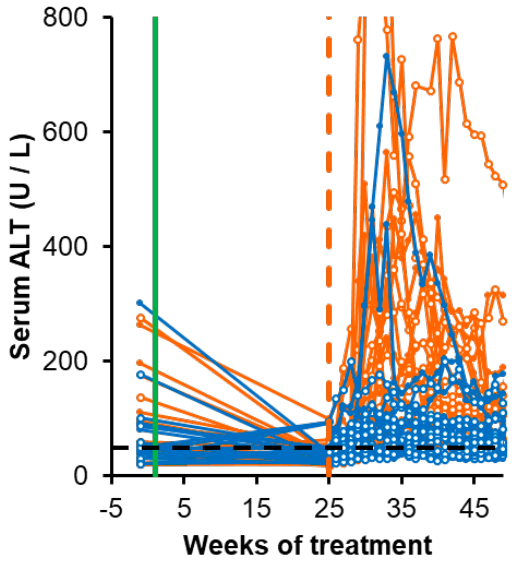
Bazinet et al., Lancet Gastroenterol Hepatol 2017; 2: 877-889 (supplemental data)
Bazinet et al., Hepatology Comm. 2020 5: 189-202

Previous HBV efficacy (REP 401 study)



Targeting of SVP from cccDNA and integrated HBV DNA
7 log_{10} decline from baseline
(to < 0.005 IU/mL)

Rapid HBsAg seroconversion (> 200,000 mIU/mL)



Dramatic increase in host mediated, otherwise asymptomatic transaminase flares

Correlated with functional cure (when HBsAg is also < 1 IU/mL)

Signals the removal of cccDNA and integrated HBV DNA

48 weeks with no therapy:
Clinical benefit (no therapy required) = 78%
Functional cure = 39%

Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Bazinet et al., J Viral Hep 2021; 28: 817-825
Bazinet et al., Hepatol Comm 2021; 28: 817-825

Replicor compassionate access program

Compassionate access to REP 2139-Mg (RCAP, NCT05683548) in eligible patient populations worldwide

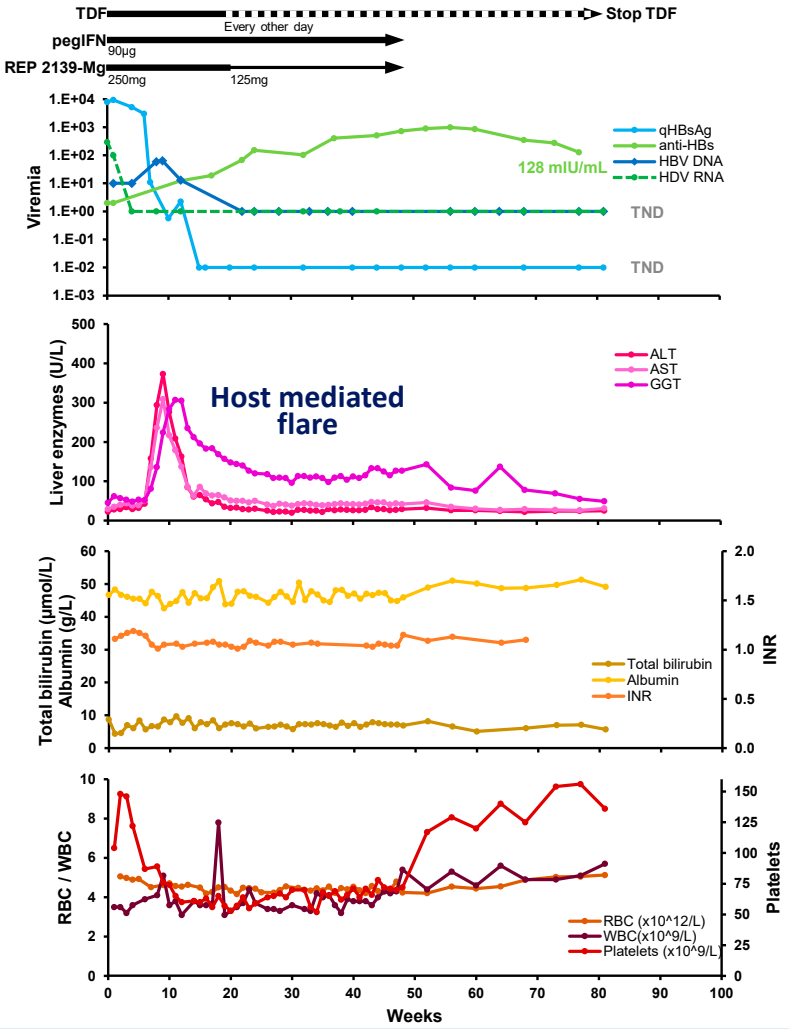
- HBV / HDV with previous failure to pegIFN, bulevirtide and lonafarnib
- HBV / HDV decompensated cirrhosis
- HBV with compensated or decompensated cirrhosis
- TDF + Weekly 250mg REP 2139-Mg SC with 90µg pegIFN (only with compensated cirrhosis).

Current enrollment:

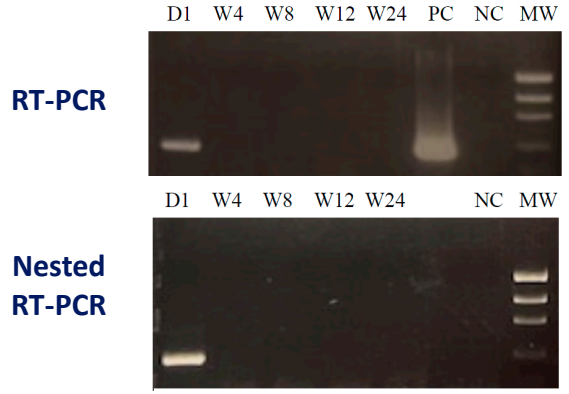
- France (17 patients, 8 centers) – available data presented today
- Israel (1 patient, 1 center)
- Austria (3 patients, 1 center)
- Turkey (4 patients, 1 center)
- Italy (1 patient, 1 center)
- Australia (1 patient, 1 center)

Activity in bulevirtide failure patients
(therapy completed)

Senegalese male, 51
HDV GT-5, cirrhosis
Previous failure on pegIFN + BLV



Pan-genotypic HDV RT-PCR confirming HDV RNA response in Patient 1

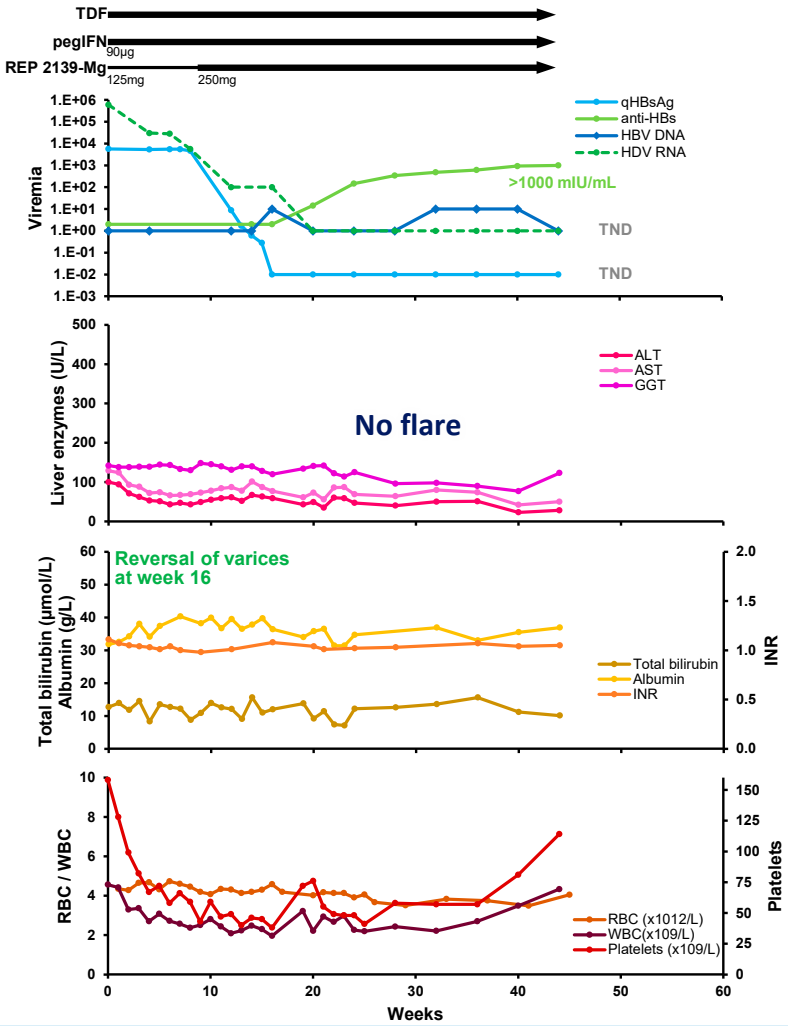


HBsAg, HDV RNA TND and HBsAg seroconversion maintained 8 months after withdrawal of REP 2139-Mg and pegIFN

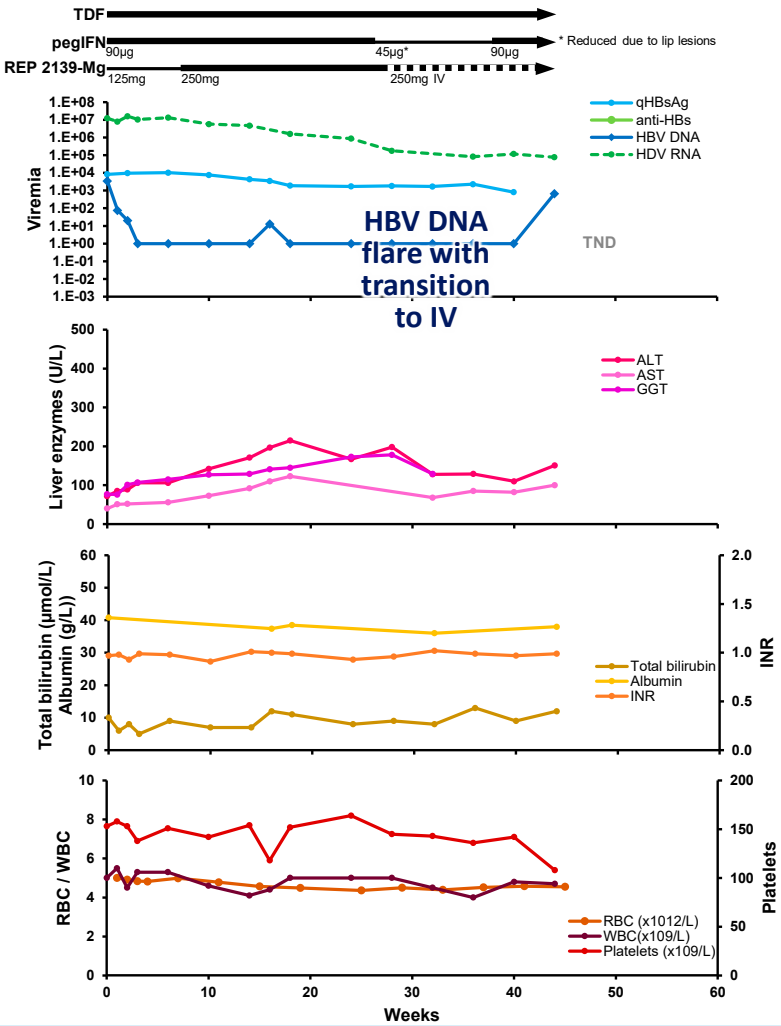
TDF now withdrawn

Activity in bulevirtide failure patients
(> 24 weeks exposure)

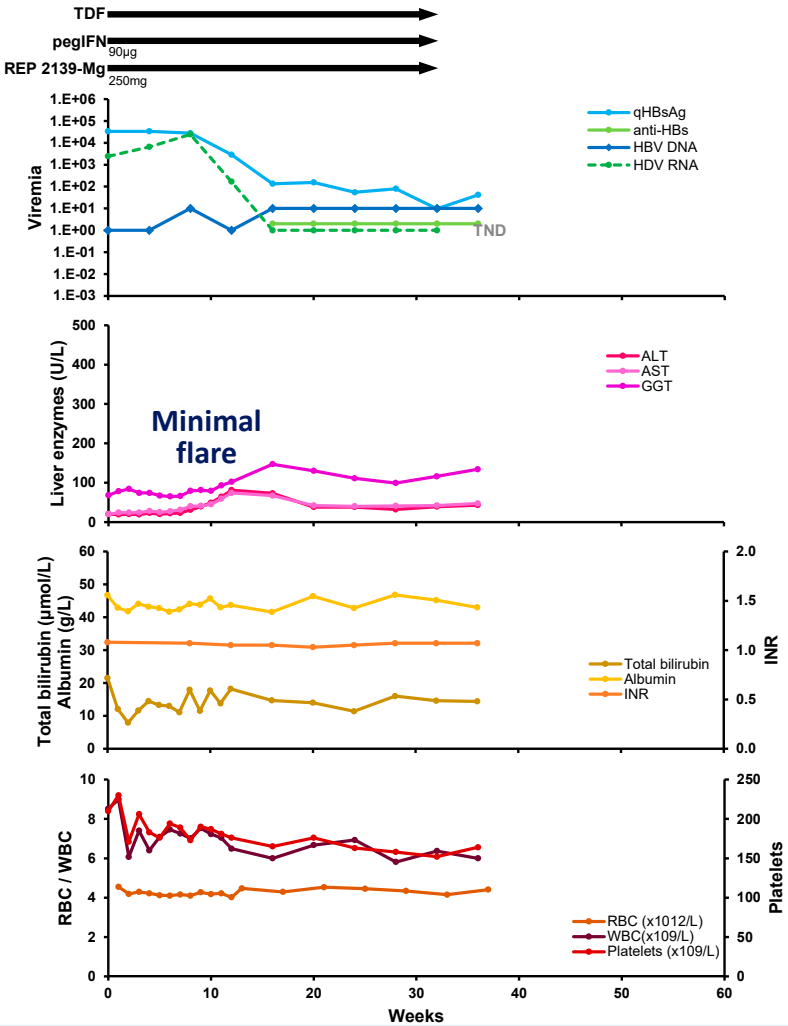
Caucasian male, 47
HDV GT-1, cirrhosis, stage 1 varices
Previous failure on pegIFN + BLV



Asian male, 54
HDV GT-1, cirrhosis
BMI 30
Previous failure on pegIFN + BLV

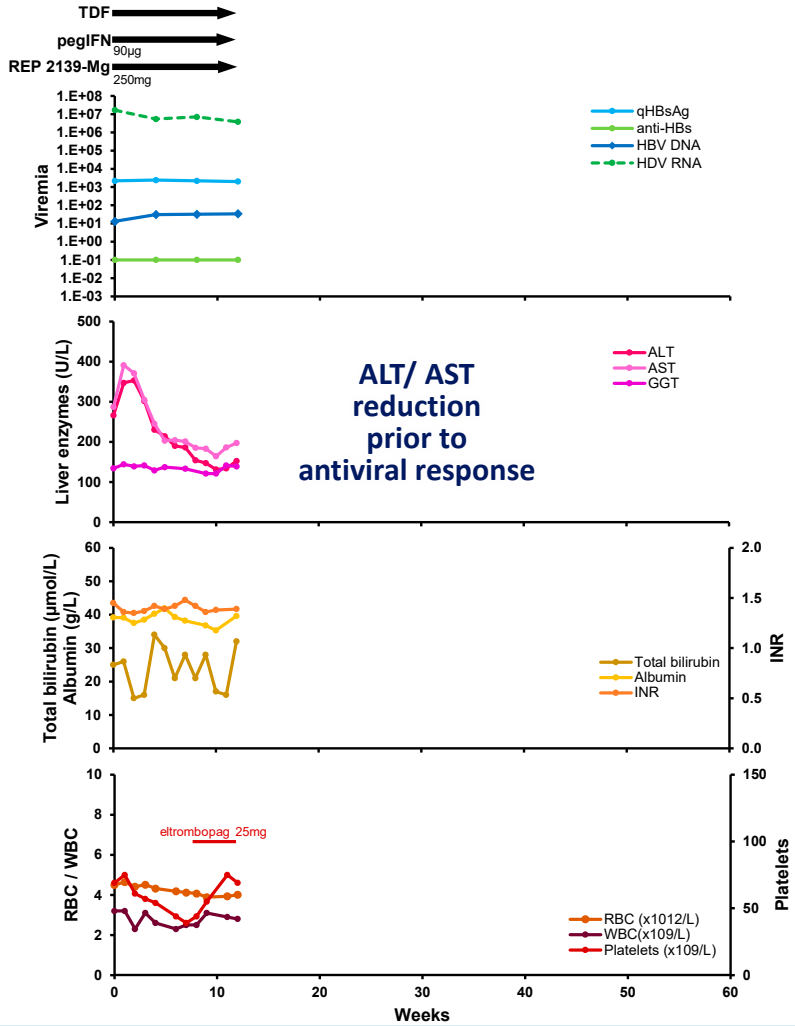


Caucasian female, 59
HDV GT-1, cirrhosis
Previous failure on pegIFN + BLV

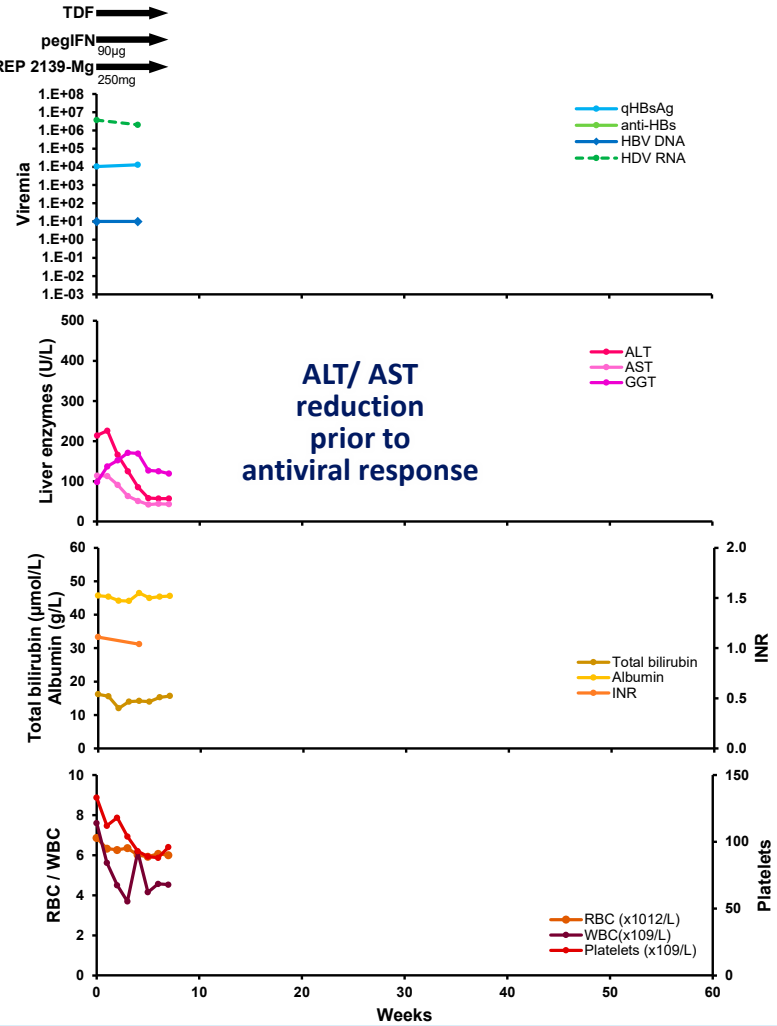


Activity in bulevirtide failure patients
(< 24 weeks exposure)

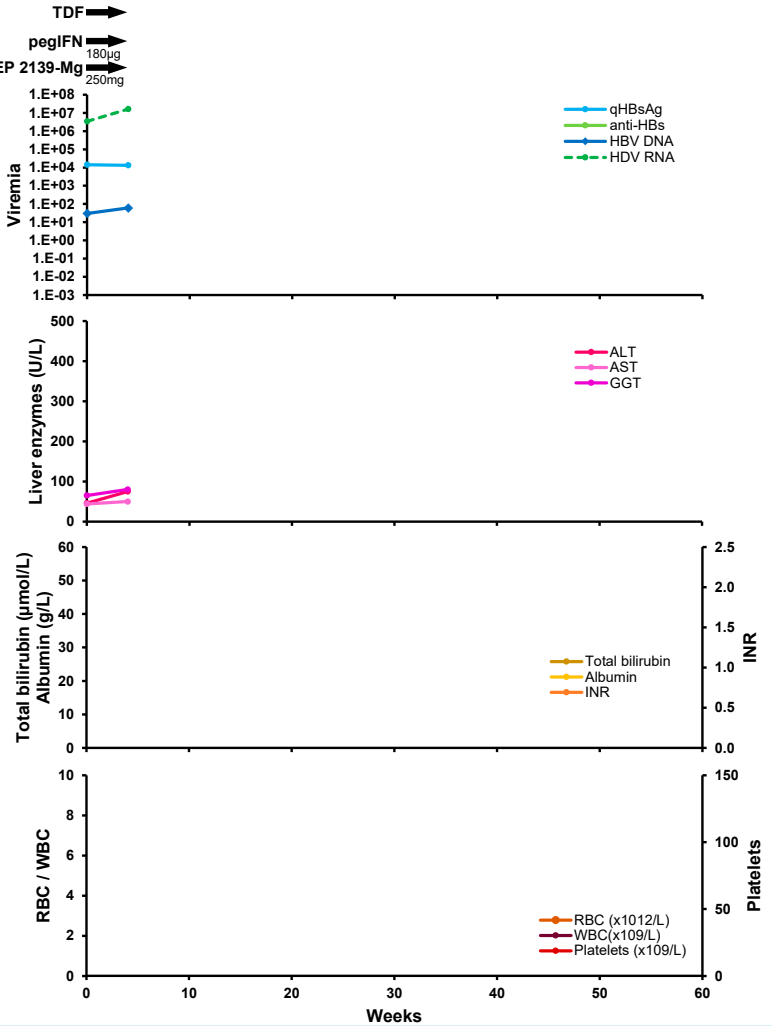
Caucasian male, 36
HDV GT-1, cirrhosis
Previous failure on pegIFN + BLV



Caucasian male, 50
Cirrhosis
Previous failure on pegIFN + BLV

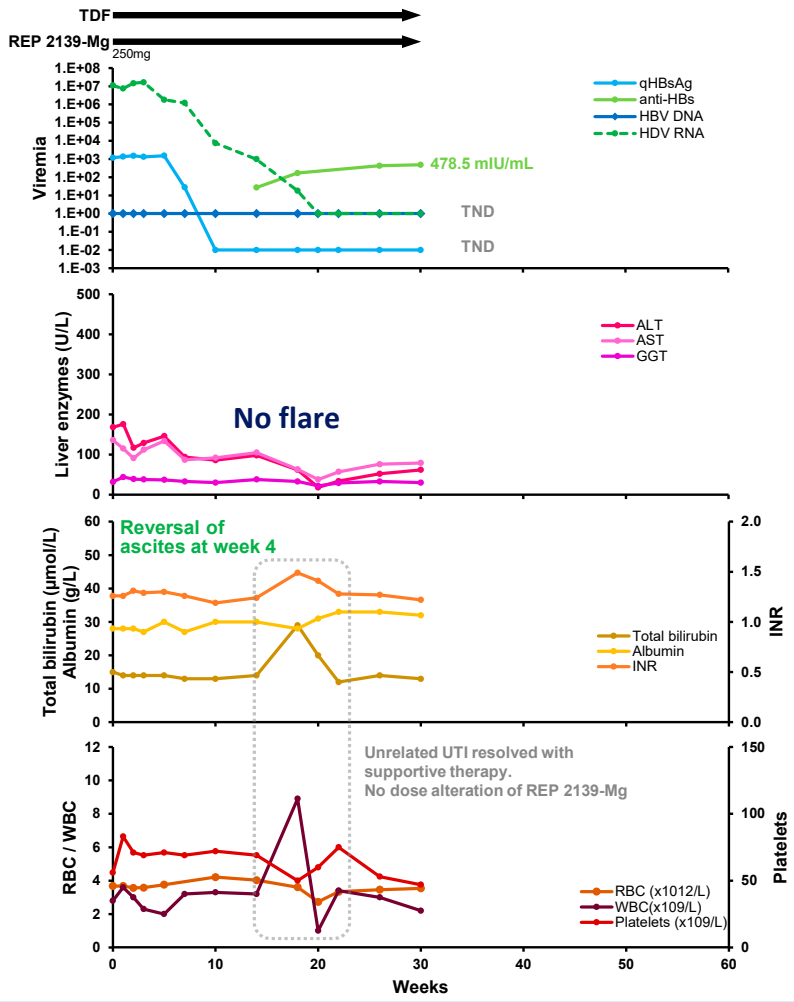


Caucasian male, 45
Cirrhosis
Previous failure on pegIFN + BLV

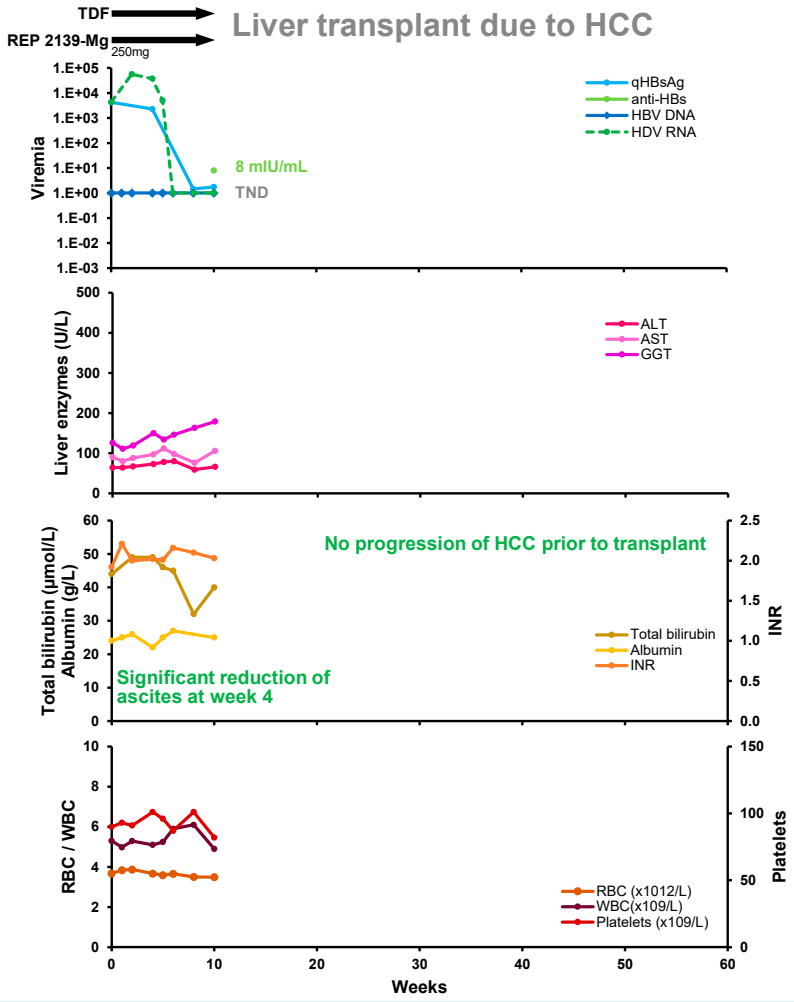


Activity / safety in decompensated cirrhosis
(see poster PPB-014 / OC-29)

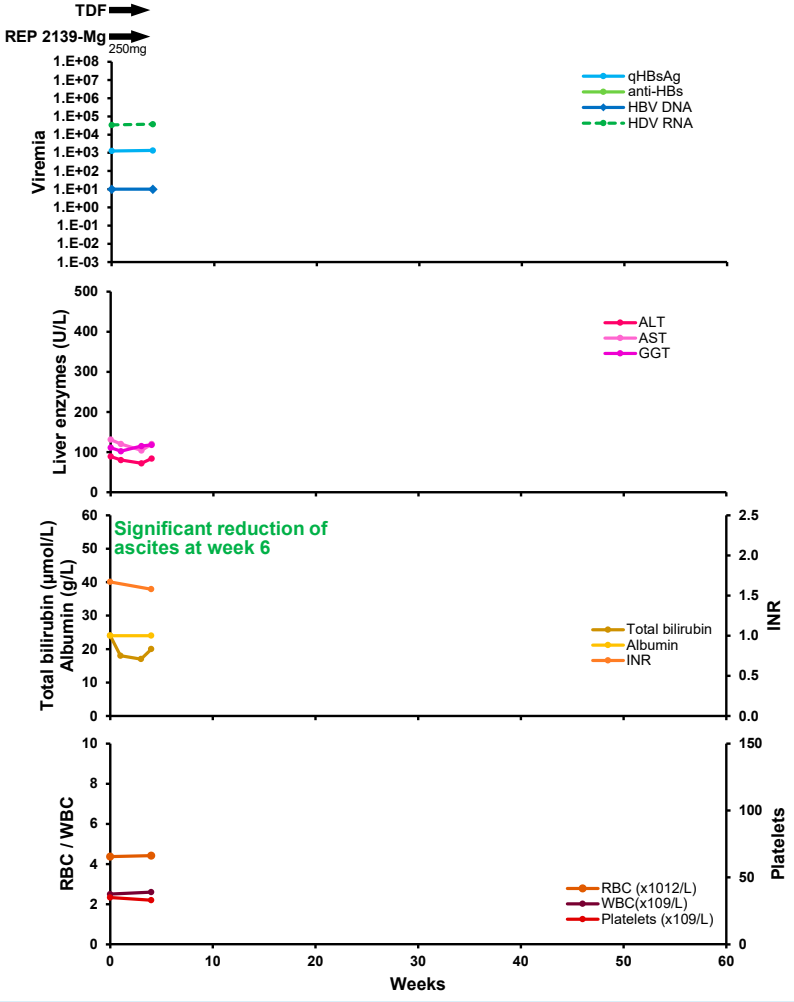
Caucasian female, 56
HDV GT-1, decompensated cirrhosis with ascites



African female, 56
HDV GT-5, decompensated cirrhosis with ascites
Arterial hypertension, diabetes, HCC



African male, 47
Decompensated cirrhosis with ascites
Arterial hypertension, diabetes



Safety / tolerability

No drug related AE's to date (compensated or decompensated cirrhosis)

SC injection of REP 2139-Mg is well tolerated

- Mild transient induration / itching / tingling in some patients
- Many patients are now performing self injection on an outpatient basis

Summary

SC REP 2139-Mg is well tolerated and safe in compensated and decompensated cirrhosis

New safety envelope expands REP 2139-Mg use to all HBV and HBV / HDV patients

HBsAg and HDV RNA loss observed in previous REP 301 / 401 studies are replicated

- Including in bulevirtide failure patients

Early declines in ALT/AST and reversal / reduction of ascites prior to antiviral response are common

- Evidence of early anti-inflammatory / hepatoprotective effects of NAPs

Lack of ALT/AST flares may reflect altered immunological status in cirrhotic livers

- Present with NAPs + pegIFN in non-cirrhotic patients

Functional cure of HBV and HDV is possible in these special patient populations

All upcoming phase II trials for HBV and HBV / HDV infection will transition to SC administration