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

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Disclosures

- Consultant : Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept, Precision BioSciences

- Speaker : Roche, Schering-Plough, Merck, Janssen, Gilead, BMS, AbbVie, Intercept

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

  Up to 56% functional cure at 5.3 years

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

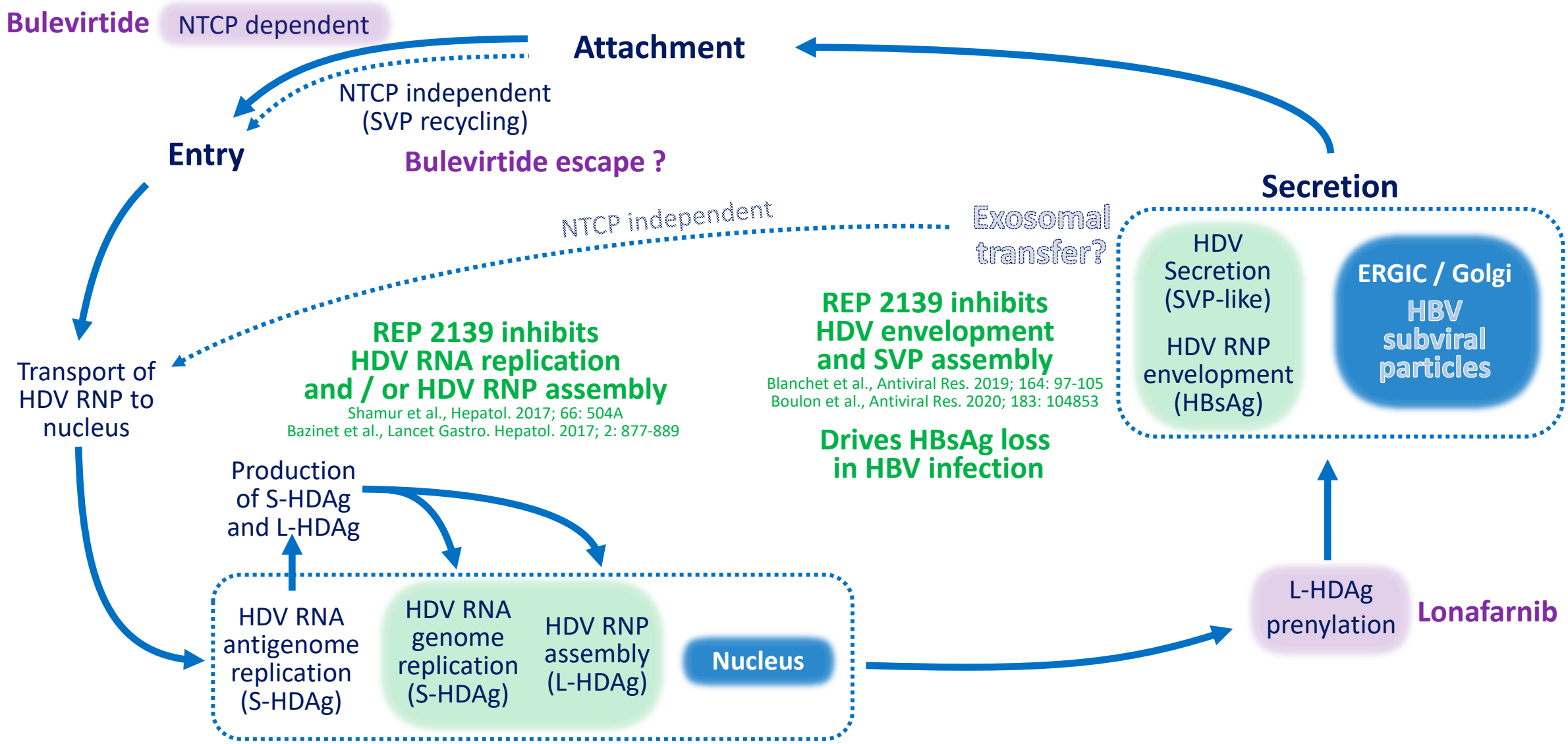
- Achieves HDV RNA loss in 100% of patients in a previous phase II trial
- Combined with pegIFN in a suboptimal regimen in HBV / HDV co-infection:

  64% of patients with undetectable HDV RNA and normal liver function at 7.4 years follow-up

  All with functional or partial cure of HBV at 7.4 years

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
Bazinet et al., GHS 2023 LB O105

Targeting HDV replication with REP 2139



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

One approved agent: bulevirtide (blocks NTCP-dependent HDV entry)

Non-response or viral rebound occurs in a significant number of patients

Replicor compassionate access program

Compassionate access to REP 2139-Mg (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 daily + Weekly 250mg REP 2139-Mg SC with 90µg pegIFN (only with compensated cirrhosis)**
- **Scheduled treatment duration of 48 weeks**

Current enrollment: 33 patients

- France (18 patients, 8 centers) – available data presented today
- Israel (1 patient, 1 center)
- Austria (3 patients, 1 center)
- Turkey (4 patients, 1 center)
- Italy (4 patients, 1 center)
- Germany (1 patient, 1 center)
- Australia (1 patient, 1 center)
- Canada (1 patient, 1 center)

Baseline characteristics
(in patients with ≥ 4 weeks of therapy completed)

Parameter	Mean (range) where applicable
Number	**11**
Age	**44.7** (21-59)
Sex	**4 female, 7 male**
Ethnicity	**8 Caucasian** **1 African** **1 Asian** **1 Central Asian**
Liver status	**9 Compensated cirrhosis** (CP A5: 6, A6: 1, B7: 1, one unknown) **2 F3-F4 Fibrosis**
HBeAg status at baseline	**8 negative, 3 positive**
HDV genotype (Done centrally at Hôptial Avicenne)	**6 genotype 1** **1 genotype 5** 4 genotypes to be assessed
HDV RNA (IU/mL)	**3.59 x10^{6}** (295-1.68x10^{7})
HBsAg (IU/mL)	**11759.58** (2200-33559)
HBV DNA (IU/mL)	**320.6** (TND-3440*)
ALT (U/L)	**93.4** (20-266)
Bilirubin (µmol/L)	**14.9** (8-34)

*TDF therapy started at baseline

Virologic response with TDF+ REP 2139-Mg SC + 90µg pegIFN

Virologic response	Duration of therapy							
	1-4 weeks (n=8)	5-8 weeks (n=8)	9-12 weeks (n=8)	13-24 weeks (n=5)	24-48 weeks (n=4)	> 48 weeks (n=1)*	Removal of NAP + pegIFN (n=2)	Removal of TDF (n=1)
HDV RNA ≥ 2 log decline from baseline		1	2	0	1	1	0	0
HDV RNA TND **	1	1	1	3	3		2	1
HBsAg > 1 log decline from baseline			1		1		0	0
HBsAg > 2 log decline from baseline		1	2	1	1	1	0	0
HBsAg < 0.05 IU/mL			1	2	2		2	1
Anti-HBs seroconversion			1	2	2		2	1
ALT normal				2	2		2	1

*treatment extension in a patient (#3) with high BMI currently ongoing (500mg IV qW REP 2139-Mg)
**measured by Eurobioplex assay.

Virologic response with TDF+ REP 2139-Mg SC

TDF →

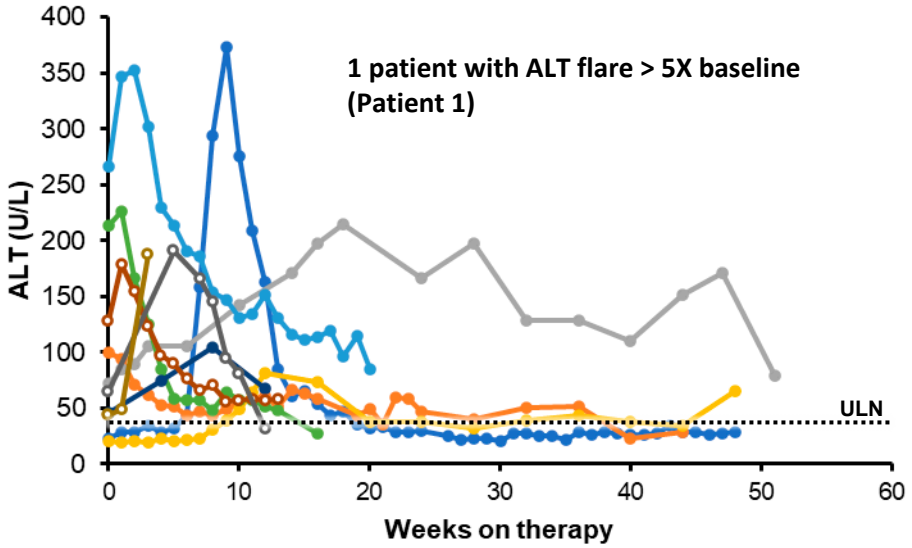
REP 2139-Mg 250mg weekly SC →

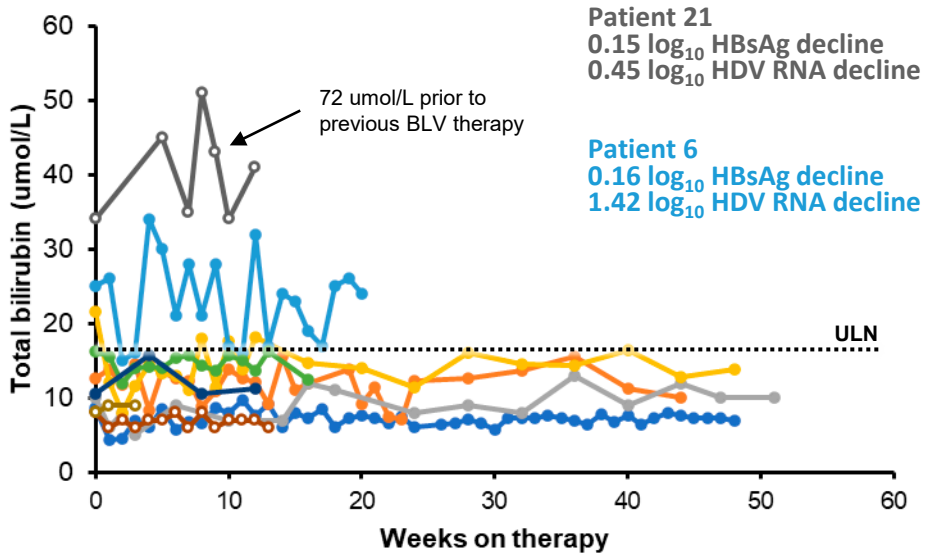
Virologic response	Duration of therapy			
	1-4 weeks (n=3)	5-8 weeks (n=3)	9-12 weeks (n=2)	13-24 weeks (n=0)
HDV RNA ≥ 2 log decline from baseline	0	1	0	
HDV RNA TND **	0	0	0	
HBsAg > 1 log decline from baseline	0	0	1	
HBsAg > 2 log decline from baseline	0	0	0	
HBsAg < 0.05 IU/mL				
Anti-HBs seroconversion				
ALT normal			1	

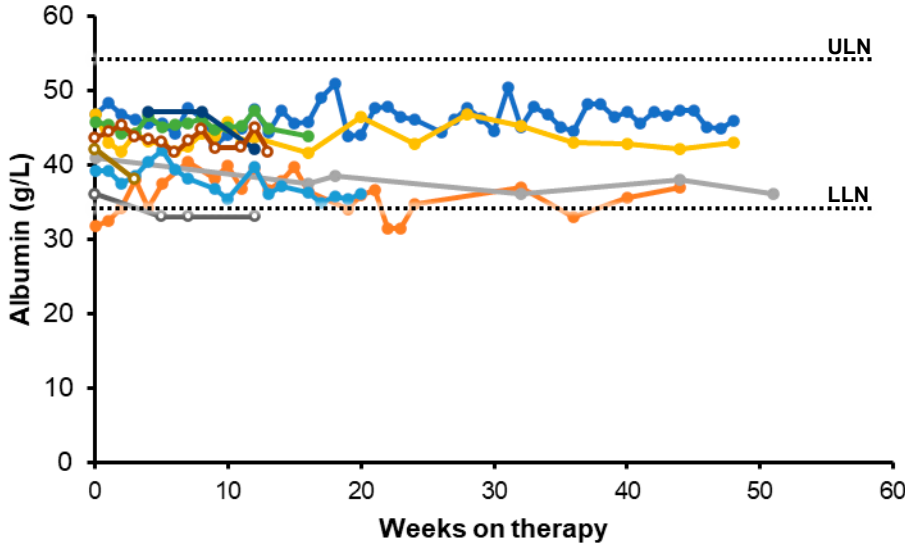
**measured by Eurobioplex assay.

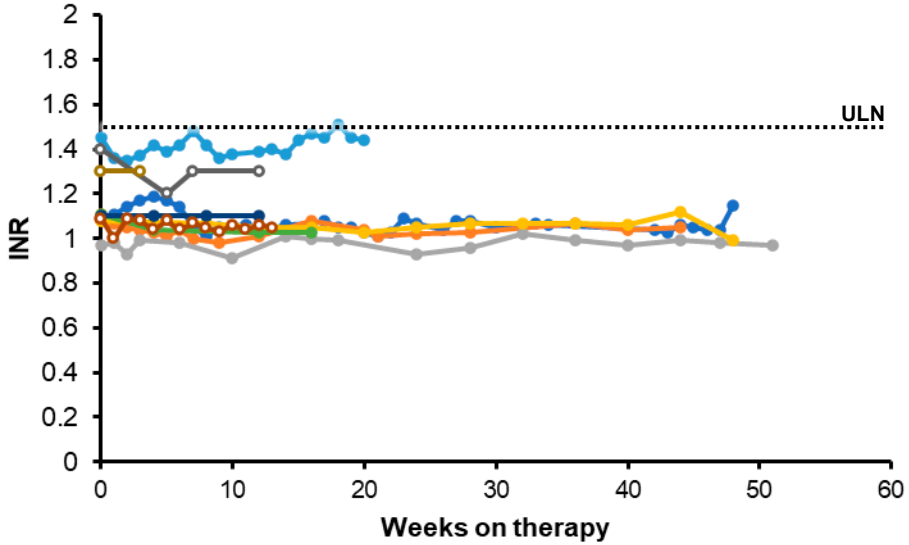
Impact on liver function

Patient number
(in order of RCAP enrollment)
- 1
- 2
- 3
- 4
- 6
- 7
- 10
- 14 (no pegIFN)
- 21 (no pegIFN)
- 22 (no pegIFN)









Administration tolerability

Patient	Injection site reactivity
1	grade 1 puritis at week 6, transient grade 1 erythema at week 13, transition to IV at week 16
2	none
3	intermittent, rapidly resolving grade 1 erythema
4	grade 1 persistent erythema
6	very rapidly resolving tingling sensation after injection
7	none
10	none
14	intermittent and transient grade 1 puritis and erythema
21	transient grade 1 puritis and erythema
22	transient grade 1 erythema
25	intermittent, transient mild pain at the injection site

Supportive therapy: topical / oral antihistamine and or low dose topical steroid

6/11 grade 1 erythema

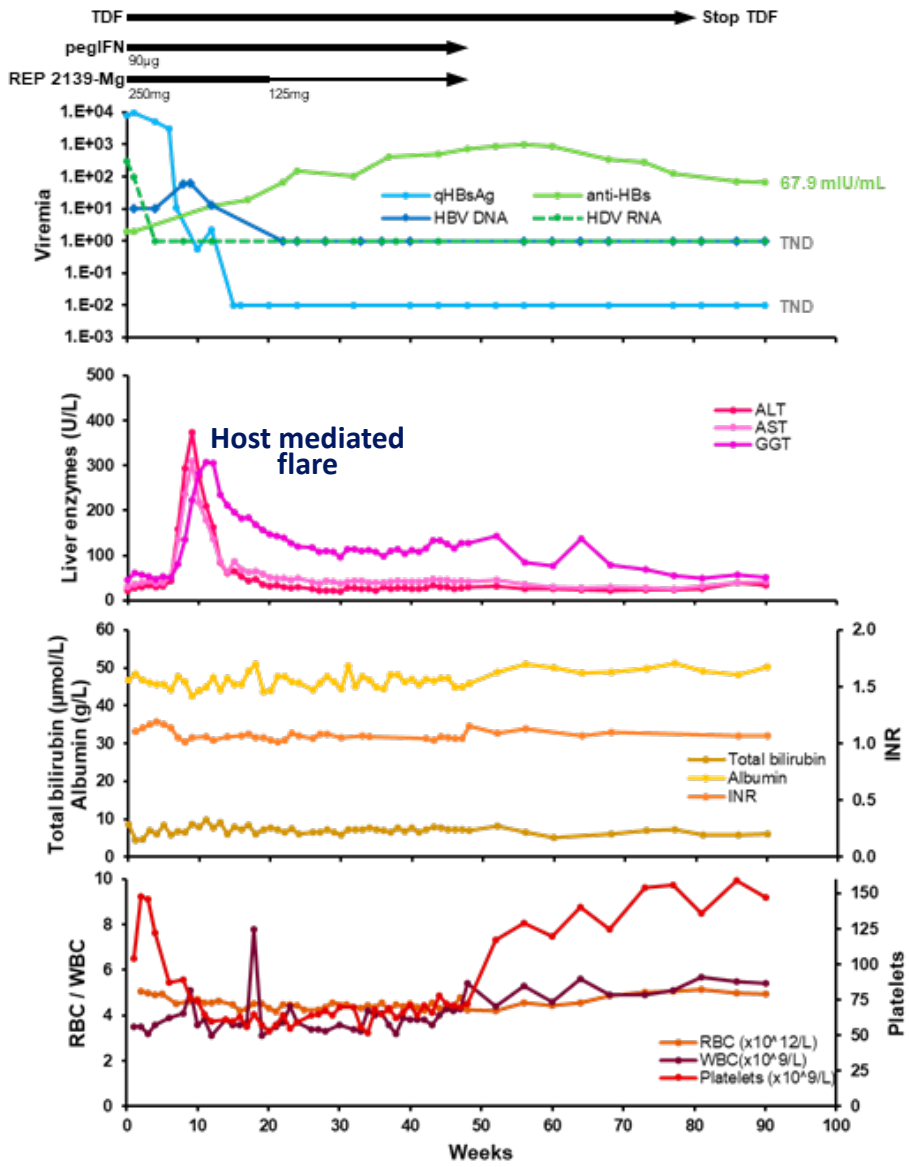
Antiviral control after completion of therapy
(case 1)

Patient 1

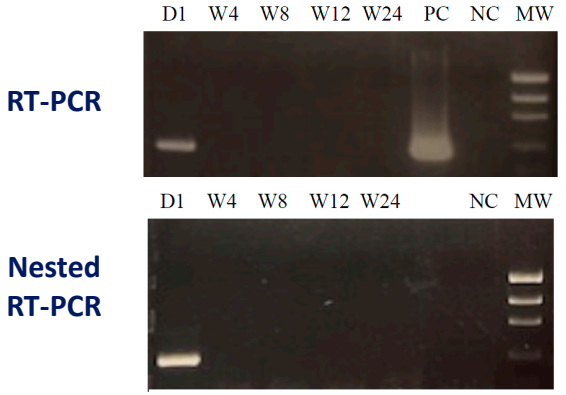
Senegalese male, 51

HDV GT-5, cirrhosis

Previous failure on pegIFN + BLV



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

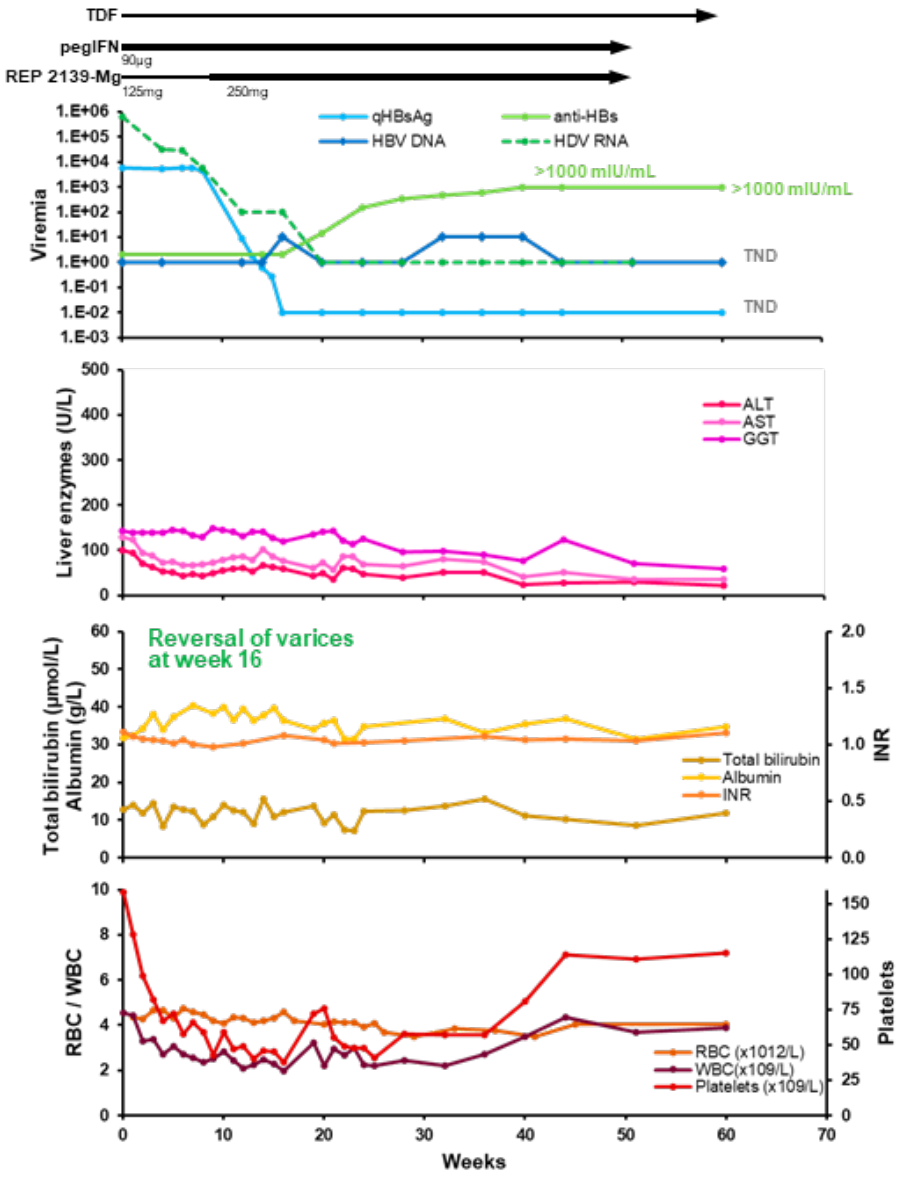


HBsAg, HDV RNA TND and HBsAg seroconversion maintained 10 months after withdrawal of REP 2139-Mg and pegIFN

TDF now withdrawn for two months with HBV DNA TND

Antiviral control after completion of therapy
(case 2)

Patient 2
Caucasian male, 47
HDV GT-1, cirrhosis, stage 1 varices
Previous failure on pegIFN + BLV



HBsAg, HDV RNA TND and HBsAg seroconversion maintained 2 months after withdrawal of REP 2139-Mg and pegIFN

Summary

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

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

- Frequent with NAPs + pegIFN in non-cirrhotic patients

Functional cure of HBV and HDV is possible in this special patient population

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