Safety and efficacy of REP 2139-Mg in association with TDF in patients with chronic hepatitis delta and decompensated cirrhosis

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Conflict of interest

- Consultant: EchoSens
- Stock options/honoraria: Gilead

Chronic hepatitis D and decompensated cirrhosis

- Chronic hepatitis D (CHD) is the most severe form of chronic viral hepatitis
- Fibrosis progression to cirrhosis is commonly observed despite HBV treatment
- No approved antiviral therapies for CHD patients with decompensated cirrhosis
- Liver transplantation is the only treatment option if decompensated cirrhosis

HBV EASL CPG, J Hepatol 2017.
Rizzetto M, Liver Int 2016.

REP 2139-Mg is safe in compensated HDV cirrhosis

Nucleic acid polymers (e.g. REP 2139) have a dual activity in HBV / HDV:

- Block HBV SVP assembly from cccDNA or integrated HBV DNA and block the envelopment of HDV RNP
- Direct interaction with HDAg likely drives observed upstream antiviral activity against HDV

Completed phase II studies demonstrate durable effects in HBV and HDV:

- **REP 401 study (HBV mono-infection, 5.3 years after therapy)**
  - 78% with immune control, normal liver function, reduction and/or normalization of liver stiffness
  - Up to 56% functional cure of HBV
- **REP 301 study (HBV / HDV infection 7.4 years after therapy)**
  - 64% (7/11) HDV RNA undetectable with normal liver function with reduction and/or normalization of liver stiffness
  - 4 with functional HBV cure, 3 with partial cure

Bazinet et al., GHS 2023, LB O105

Replicor compassionate access program

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

- HBV / HDV with previous failure to pegIFN, bulevirtide and lonafarnib
- HBV / HDV decompensated cirrhosis
- HBV with compensated or decompensated cirrhosis

Current enrollment:

- France (18 patients, 8 centers) – available data in decompensated patients 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)

Objectives

- To evaluate the efficacy and safety of REP 2139-Mg in CHD patients with decompensated cirrhosis

Patients and methods

- CHD patients with decompensated cirrhosis (Child-Pugh B or C) that have been evaluated for liver transplantation in Beaujon hospital since June 2022 were eligible for the French compassionate access program (ATU approved by ANSM)
- All patients received the following treatment for a planned duration of 48 weeks:
  - **REP 2139-Mg 250 mg QW SC**
  - **Tenofovir Disoproxil Fumarate (TDF) 245 mg QD PO**
- Clinical and biological data were collected at baseline, every week for the first 4 weeks then every month for all patients.

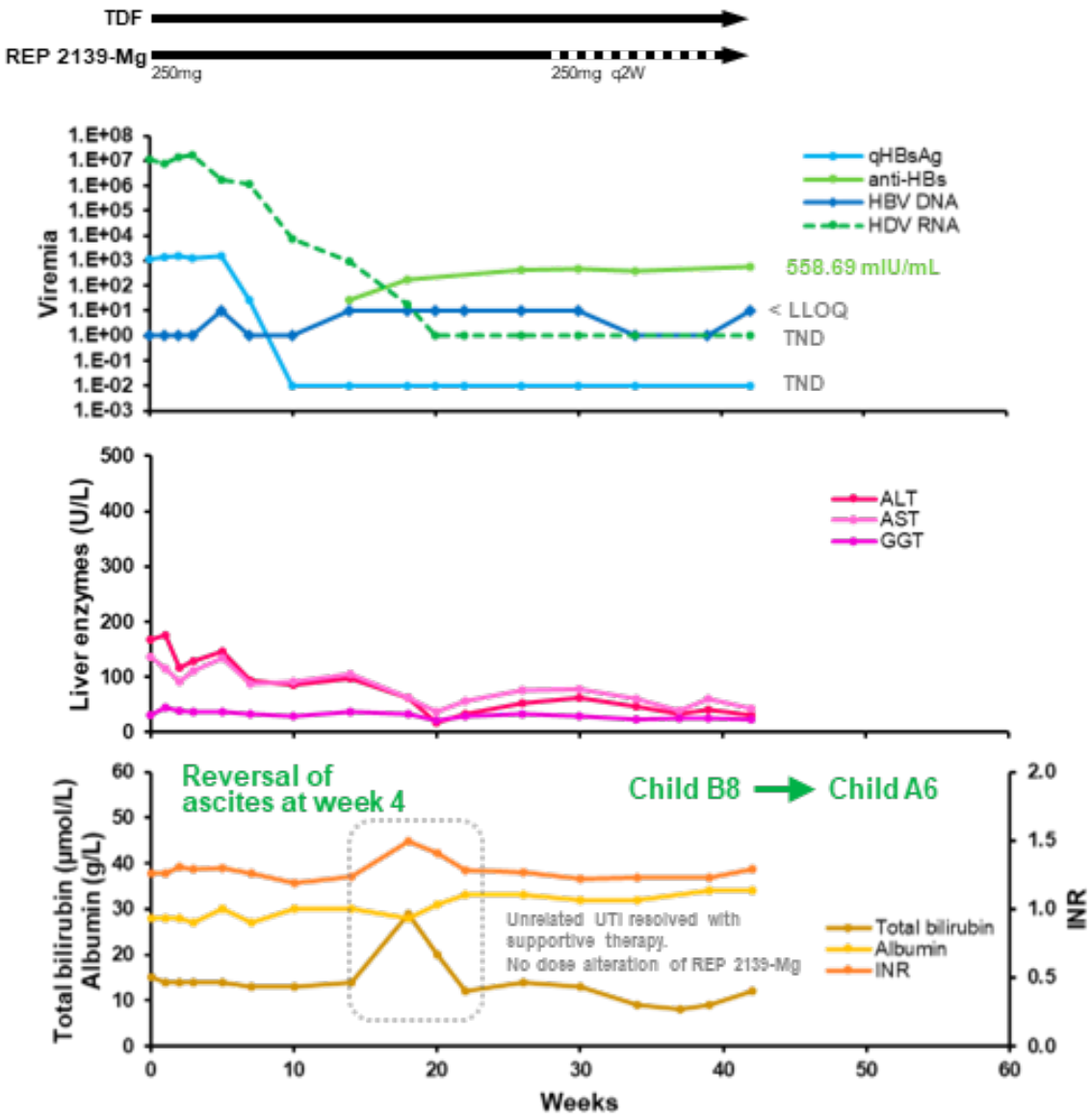
Patient baseline characteristics

Patient	1 (RCAP 5)	2 (RCAP 8)	3 (RCAP 11)
Age (years)	56	56	47
Sex	Female	Female	Male
Ethnicity	Caucasian	African	African
ALT (U/L)[#]	168	64	89
Total bilirubin (μmol/L)	15	44	24
Albumin (g/L)	28	24	24
Platelets (10^9/L)	56	90	35
INR	1.26	1.92	1.67
Child-Pugh / MELD	B8 / 9	C12 / 17	C10 / 13
HDV genotype*	1	5	5
HDV RNA (IU/mL)	$1.09x10^7$	4285	34138
HBsAg (IU/mL)	1177	4270	1273
HBeAg status	Negative	Negative	Positive
HBV DNA (IU/mL)	Target not detected	Target not detected	< 10 IU/mL (LLOQ)

[#]Normal ALT: <34 U/L in female and <45 U/L in male

*Done centrally at Hôpital Avicenne

Patient 1: 56 yo, female patient, HBV-HDV treatment-naïve

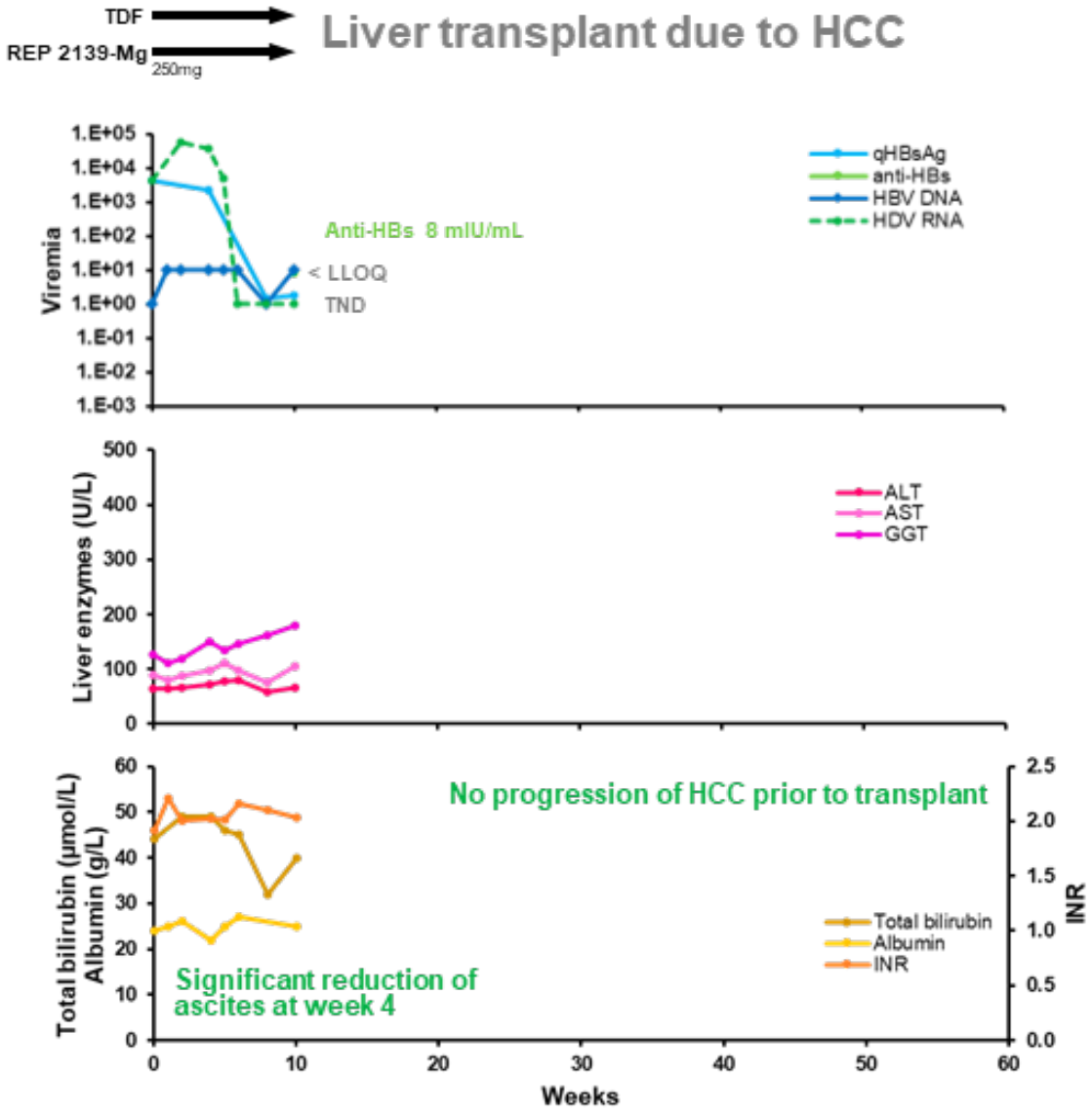


- HBsAg undetectable since W10
  (> 4.37 $\log_{10}$ IU/mL decline from baseline)
- Anti-HBs seroconversion since W14
- HDV RNA undetectable since W20

- ALT normalisation at W20

- Ascites reversal since W4
- Compensated cirrhosis since W10
- Urinary sepsis at W18 => no decomp

Patient 2: 56 yo, female patient, relapse after BLV treatment



- HDV RNA undetectable at W6
- 3.4 log_{10} IU/mL HBsAg reduction at week 8

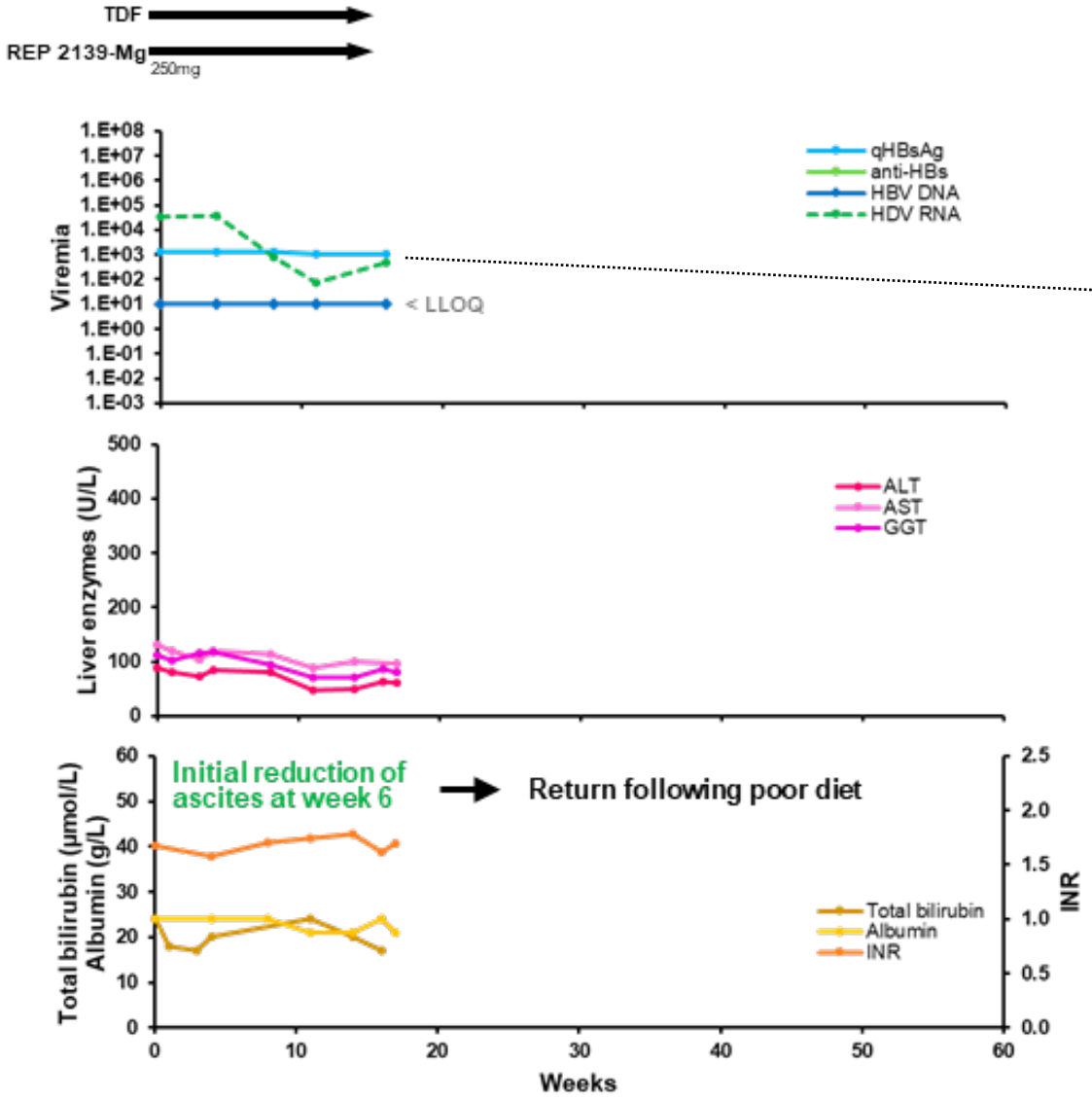
- Ascites reversal since W4
- Child-Pugh from C12 to C10 at W8

Successful liver transplantation at W10

Explant histology:

- Cirrhosis METAVIR A2 F4 (Laennec 4B)
- No steatosis
- Well-differentiated HCC nodules, no vascular emboli
- Virologic assessment of explant underway

Patient 3: 47 yo, male patient, HDV treatment-naïve



- HDV-RNA 2.7 log IU/mL decline at W11

- Albumin perfusion after paracentesis due to relapse of chylous ascites may be sequestering REP 2139
- Albumin is a known interactor for all phosphorothioate oligonucleotides including REP 2139

Gaus et al, Nuc Acids Res 2019.
Shamur et al, Hepatology 2017.

Safety and tolerance

- No hematological side effects
- No ALT flares were observed
- No general side effects related to REP 2139-Mg

Patient	Injection site reactivity
1	Transient erythema Hematoma at week 26 resolved by switching injection to every two weeks
2	none
3	none

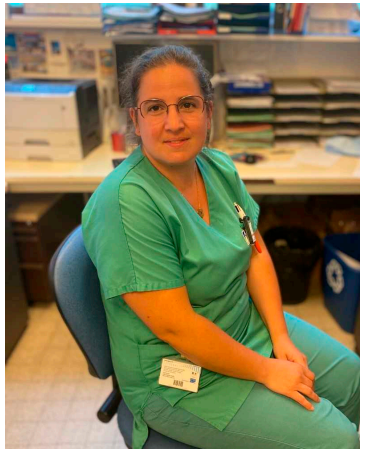
Supportive therapy (patient 1): low dose topical steroid

Conclusions

- **SC REP 2139-Mg appears well tolerated and safe in decompensated CHD cirrhosis**
  - New safety envelope potentially expands REP 2139-Mg use to all HBV and HBV / HDV patients
- **HDV RNA / HBsAg declines replicate those seen in CHD compensated cirrhosis and in previous clinical trials**
- **Lack of ALT/AST flares may reflect altered immunological status in cirrhotic livers**
  - Disconnects flare activity from direct REP 2139 exposure
- **Functional cure of HBV and HDV may be possible in patients with decompensated cirrhosis**

Acknowledgments

Therapeutic patient education nurse



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