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

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Abstract OC-29

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Introduction

Chronic hepatitis delta (CHD) typically leads to cirrhosis and hepatic decompensation. The only treatment option for CHD patients with decompensated cirrhosis is liver transplantation with associated short- and long-term complications. REP 2139-Mg is a nucleic acid polymer (NAP) that blocks the assembly and secretion of HBV subviral particles and hepatitis delta antigen function (Figure 1), providing multiple effects against both HBV and HDV infection. Compassionate access to REP 2139-Mg is being provided under the Replicor Compassionate Access Program (RCAP, NCT05683548). The objective of this study is to describe the safety and efficacy of REP 2139-Mg in CHD patients with decompensated cirrhosis.

Patients & Methods

Compassionate use was approved in France by the ANSM in the first three European CHD patients with decompensated cirrhosis to receive REP 2139-Mg 250 mg QW subcutaneously (SC) and tenofovir disoproxil fumarate (TDF) 300 mg QD orally for a planned total duration of 48 weeks. Clinical, biological, virological and imaging data were collected at baseline and every week for the first month, then every month. Safety and tolerance were continuously evaluated. Patients are numbered in order of access to REP 2139-Mg under the RCAP.

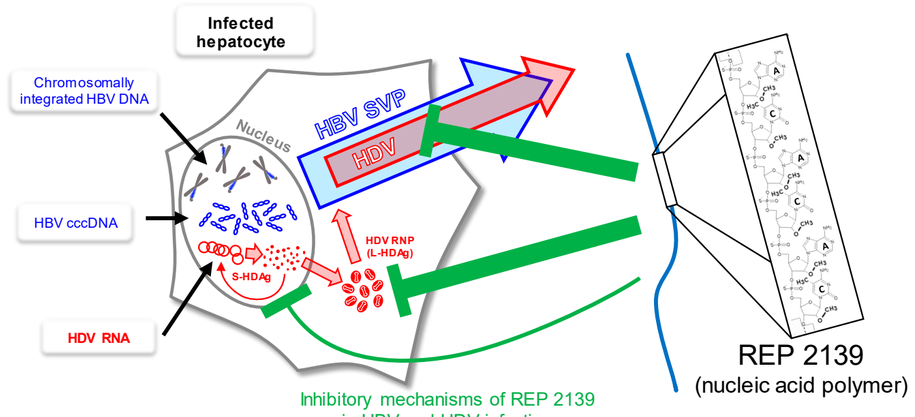


Figure 1. Antiviral mechanisms of REP 2139 in HBV and HDV infection.
REP 2139-Mg blocks the assembly of HBV subviral particles and envelopment of the HDV ribonucleoprotein (RNP) via interaction with the HSP40 chaperone DNAJB12. Direct interaction with the small and large isoforms of HDAg results in inhibition of HDV RNA replication and or HDV RNP assembly.

Boulon et al., Hepatology 2021; 74: 512A
Vaillant, ACS Inf Dis 2019; 5: 675-687
Shamur et al., Hepatology 2017; 66: 504A

Results

REP 2139-Mg has been well tolerated to date in these three patients with no adverse events. Subcutaneous injections of REP 2139-Mg have been well tolerated.

Patient 5 is a Caucasian, 56-year-old female, HDV treatment-naïve, with CHD decompensated cirrhosis (Child Pugh B8, portal hypertension and ascites) with HDV RNA 7.04 $\log_{10}$ IU/mL and HBsAg 1177 IU/mL at baseline. At week 4 of therapy, reversal of ascites was confirmed by ultrasound (minimal diuretic dose was maintained due to mild bilateral leg edema). HBsAg loss occurred at week 10 with HBsAg seroconversion (27 mIU/mL) at week 14 increasing to 478.5 mIU/mL at week 30. HDV RNA has been undetectable since week 20.

Patient 8 is an African, 56-year-old female with CHD and hepatocellular carcinoma awaiting liver transplant. She experienced HDV relapse 1 year after discontinuing bulevirtide 2 mg QD and pegIFN 180 μg QW and progressed to decompensated cirrhosis (Child Pugh C11, portal hypertension, ascites and hepatocellular carcinoma) with accompanying edema, and pronounced fatigue. Baseline HDV RNA was 3.64 $\log_{10}$ IU/mL and HBsAg 4270 IU/mL. At Week 4, abdominal CT confirmed significant reduction of clinical ascites, and peripheral edema and fatigue were markedly reduced. HDV RNA became undetectable at week 6. Successful liver transplant was performed in this patient after 10 weeks of therapy and explant analysis is underway. Prior to liver transplant (after week 10), HDV RNA was undetectable (by week 6), HBsAg was 1.75 IU/mL and anti-HBs was 8 mIU/mL.

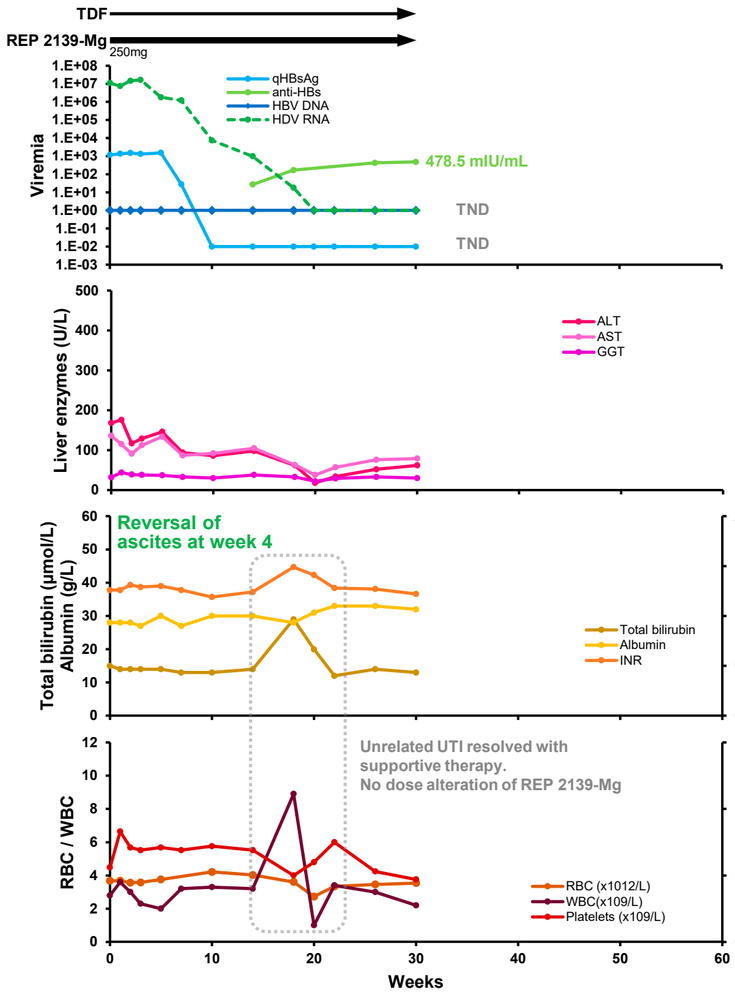
Patient 11 is an African, 47-year-old male, HDV treatment-naïve, with CHD decompensated cirrhosis (Child Pugh C10, portal hypertension, ascites, and hepatic encephalopathy) with HDV RNA 4.53 $\log_{10}$ IU/mL and HBsAg 1273 IU/mL at baseline. Early exposure to REP 2139-Mg in patient 11 is well tolerated to date.

Conclusions

1. **REP 2139-Mg in association with TDF is safe and well tolerated in patients with CHD and decompensated cirrhosis.**
2. **Liver function improvement with significant ascites reversal was rapid, occurring after only 4-6 weeks of treatment.**
3. **HBV-HDV functional cure appears achievable in this special population which could prevent the need for a future liver transplant.**

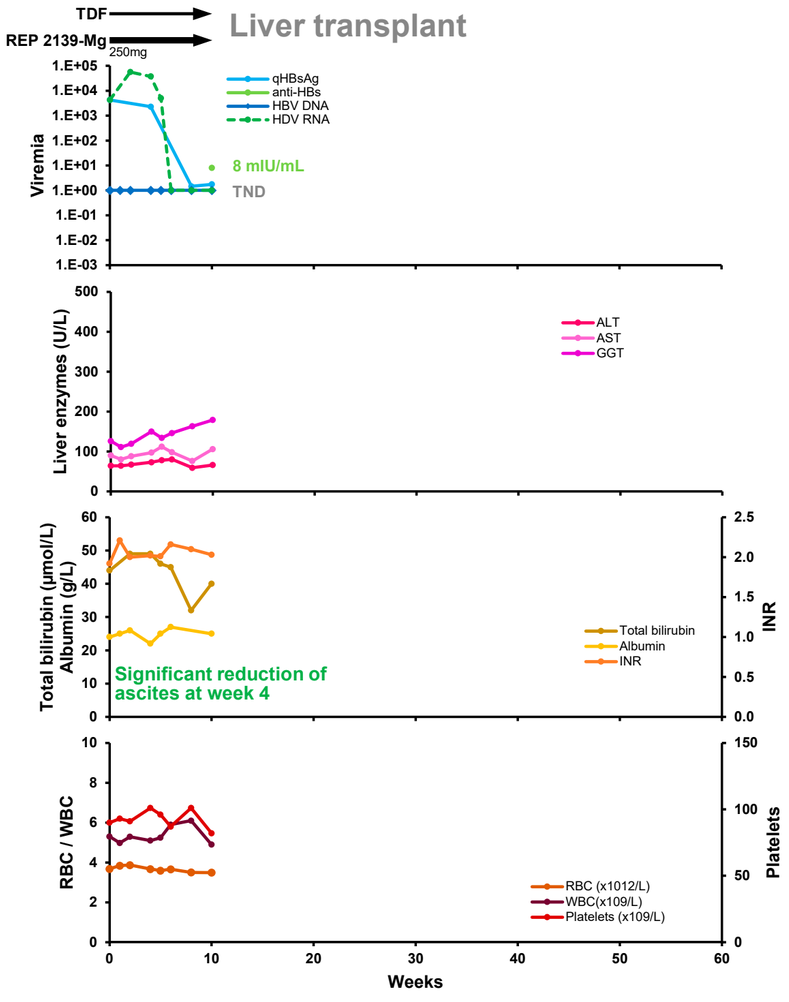
Patient 1

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



Patient 2

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



Patient 3

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