DDW2023
Digestive Disease Week®
MAY 6-9, 2023 | CHICAGO, IL
EXHIBIT DATES: MAY 7-9, 2023

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

M. Bourlière[1], V. Loustaud-Ratti[2], C. Stern[3], S. Ben Ali[1], E. Bardou-Jacquet[4], L. Alric[5], L. Colombain[6], S. Metivier[7], M. Meszaros[8], M. Bazinet[9], L. Lecomte[1], S. Francois[2], C. De-Fretias[3], A. Levacher[4], A. Sondro[5], C. Morvan[6] H. Aumatire[6], A. Gerber[10], S. Brichler[10], E. Gordien[10] A. Vaillant[9]

1. Service Hépato-Gastro-Entérologie, Hôpital Saint-Joseph, Marseille, France, 2. .Service d'Hépato-Gastroentérologie, CHU de Limoges, Limoges, France, 3. Service de Hépatologie, AP-HP Hôpital Beaujon, Clichy, France, 4. Service des Maladies du Foie, CHU de Rennes, Rennes, France, 5. Service de médecine interne-maladies digestives, CHU Rangueil, Université Toulouse 3, Toulouse, France, 6. Centre Hospitalier de Perpignan, Perpignan, France, 7. Service d'hepatologie, CHU Rangueil, Université Toulouse 3, Toulouse, France, 8. CHU Montpelier, Montpelier, France, 9. Replicor Inc., Montreal, Canada, 10. Centre national de référence des hépatites B, C et Delta – Laboratoire associé, Hôpital Avicenne, Bobigny, France

INTRODUCTION

REP 2139 blocks HBV subviral particle assembly and hepatitis delta antigen function, driving HBsAg loss in HBV infection and HBsAg / HDV RNA loss in HBV / HDV co-infection. Previous phase II clinical trials have demonstrated high rates of durable functional cure of HBV and undetectable HDV RNA with normal liver function and continually improved liver stiffness (see references) after removal of antiviral therapy.

AIM

The safety and efficacy of SC injection of REP 2139-Mg in combination therapy is currently being assessed in cirrhotic patients with chronic HBV / HDV co-infection after failure or viral rebound during bulevirtide (BLV) therapy under the Replicor Compassionate Access Program (RCAP) (NCT05683548).

METHODS

Compassionate use of REP 2139-Mg was approved by the Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France. Initial patients with chronic HBV / HDV co-infection were required to have demonstrated non-response or rebound to previous BLV therapy with compensated cirrhosis. Two subsequent patients were approved with rapidly progressing fibrosis after BLV failure. All patients provided signed informed consent prior to therapy. After at least 4 weeks of washout from BLV, existing NUC therapy was supplemented with 250mg REP 2139-Mg administered by subcutaneous injection each week with 90µg of pegIFN (unless contraindicated by previous tolerability issues). Therapy is scheduled for 48 weeks with the possibility of treatment extension. Regular safety assessments were accompanied by assessment of qHBsAg and anti-HBs (Abbott Architect©), HBV DNA (Abbott *Realtime*©) and HDV RNA (Eurobioplex) at least every 4 weeks.

Table 1. 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, 1 unknown) 2 Fibrosis (1 F2-F3, 1 F3-F4)
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) 1=TND	320.6 (1-3440*)
ALT (U/L)	93.4 (20-266)
Bilirubin (µmol/L)	14.9 (8-34)

*TDF therapy started at baseline

RESULTS

Table 2. Virologic response during therapy

Virologic response	Duration of therapy							
	1-4 weeks (n=11)	5-8 weeks (n=11)	9-12 weeks (n=9)	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		2	2		1	1		
HDV RNA TND **	1	1	1	3	3		2	1
HBsAg > 1 log decline from baseline			2		1			
HBsAg > 2 log decline from baseline		1	2	1	1	1		
HBsAg < 0.05 IU/mL				2	2		2	1
Anti-HBs seroconversion			1	2	2		2	1
ALT normal				3	2		2	1

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

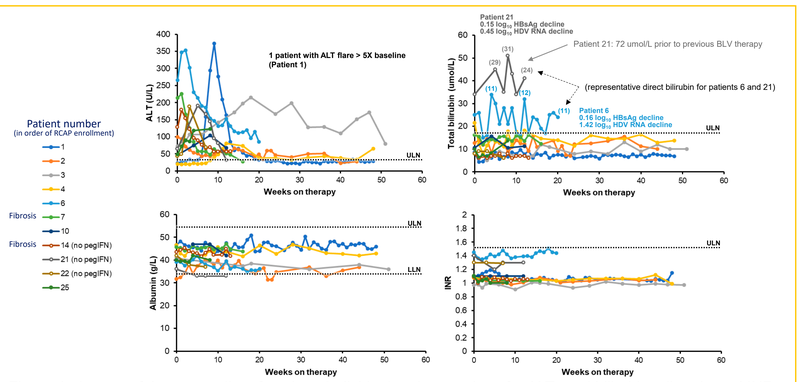


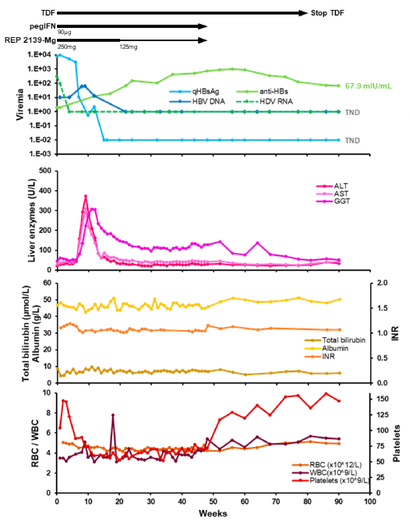
Figure 1. Impact of therapy on liver function. Individual patient tracings for ALT, total bilirubin, albumin and INR are provided. Patients not receiving pegIFN are indicated with hollow markers. Patients with fibrosis at baseline are indicated in the legend.

Table 3. 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 erythema
22	transient grade 1 erythema
25	intermittent, transient mild pain at the injection site

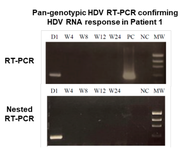
6/11 grade 1 erythema

Patient 1
Senegalese male, 51, HDV GT-5, cirrhosis
Previous failure on pegIFN + BLV

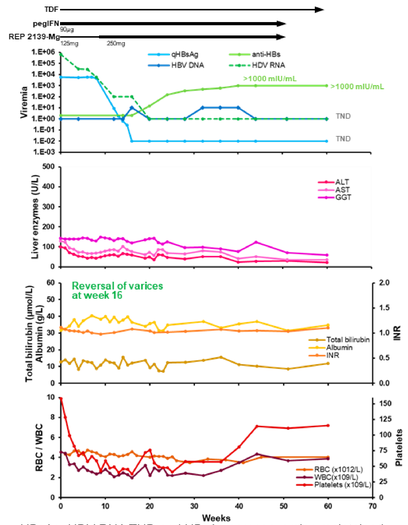


HBsAg, HDV RNA TND and HBsAg seroconversion maintained 10 months after withdrawal of REP 2139-Mg and pegIFN

TDF now withdrawn for two months with HBV DNA TND



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

Figure 2. Antiviral control in the two patients completing therapy.

CONCLUSIONS

SC REP 2139-Mg is well tolerated and safe in compensated cirrhosis
- New safety envelope expands REP 2139-Mg use to cirrhotic 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 in some patients may reflect altered immunological status in cirrhotic livers
- Flares are 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

REFERENCES

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

CONTACT INFORMATION

mbourliere@hopital-saint-joseph.fr

availlant@replicor.com