Establishment of persistent functional remission of HBV and HDV infection following REP 2139-Ca and pegylated interferon alpha-2a therapy in patients with chronic HBV / HDV co-infection: 1.5 - 2 year follow-up results from the REP 301-LTF study

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THE INTERNATIONAL LIVER CONGRESS™ 2018

APRIL 11-15, PARIS, FRANCE

INTRODUCTION

REP 2139 is a nucleic acid polymer which blocks the assembly / secretion of HBV subviral particles[1] and additionally binds to the small and large forms of HDAg[2] (see Fig. 1). In the previous REP 301 study (NCT02233075)[3] combination therapy with REP 2139-Ca and pegIFN in patients with HBV/HDV co-infection was well tolerated and achieved > 5 log reduction in HDV RNA in 12/12 patients and HDV RNA target not detected in 11/12 patients. Additionally, 9/12 patients achieved HBsAg reduction > 1 log from baseline and 5/12 patients achieved HBsAg loss. During the initial 1 year follow-up in the REP 301 and REP 301-LTF (NCT02876419) studies, 7/12 and 5/12 patients had undetectable HDV DNA and HBsAg. Evolving follow-up data is presented from the ongoing REP 301-LTF study.

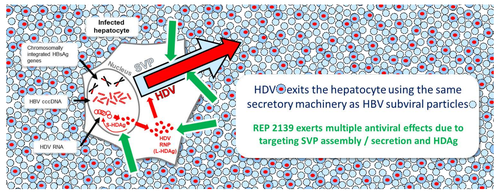

Figure 1. Antiviral mechanisms of REP 2139 in HDV infection.

AIMS

- To evaluate the long term safety of combination therapy with REP 2139-Ca and pegIFN.
- To evaluate the durability of the functional remission of HBV and HDV infection achieved in the REP 301 study.

METHODS

REP 301 patients (see Table 1) completing therapy were enrolled in the REP 301-LTF trial. Patients will be followed every 6 months for a period of 3 years. HDV RNA, HBV DNA, HBsAg and anti-HBs are followed every 6 months using standard assays (Robogene MK II RT-PCR, Abbott RealTime HBV, Abbott Architect). Median hepatic stiffness is evaluated by Fibroscan.

Table 1. Pre-treatment demographics of patients enrolled in the REP 301 / REP 301-LTF studies.

Patient	Age	Sex	ALT (U/L)	Median Hepatic Stiffness (kPa)	HBsAg (IU/mL)	HBV DNA (IU/mL)	HBV RNA (log copies/mL)	HBcrAg (log U/mL)	HDV RNA (IU/mL)	Duration of HDV infection prior to treatment
001-01	33	F	188	8.4	13988	< 10	TND	< LLOD	394000	1 year, 5 months
001-02	29	F	98	7.7	27264	<10	TND	< LLOD	47100000	3 years, 6 months
001-03	40	M	53	14.8	28261	< 10	TND	< LLOD	697000	18 years
001-06	37	M	95	6.8	17511	726	TND	4.1	5490000	12 years
001-09	22	M	85	12.0	16426	104	1.73	4.4	211000	4 years, 7 months
001-11	35	M	200	9.6	12382	<10	TND	3.2	12100000	9 years
001-14	32	M	143	11.6	20869	<10	TND	< LLOD	23000000	6 years, 1 month
001-17	34	M	62	9.5	8314	350	TND	< LLOD	1690000	10 months
001-20	44	F	29	8.8	13430	<10	TND	4.5	27400	12 years
001-22	36	M	101	11.9	7836	16	2.22	5	1090000	1 year, 6 months
001-24	39	M	160	7.8	20473	<10*	TND	2.8	1890000	4 years, 10 months
001-26	39	M	85	30.7	5854	256	TND	4.5	3760000	9 years

Table derived from (1). All patients were HDV genotype 1, HBeAg negative and anti-HBe positive.
Patient 01-014 was excluded from enrollment in the REP 301-LTF study as therapy was terminated early in this patient[1].

RESULTS

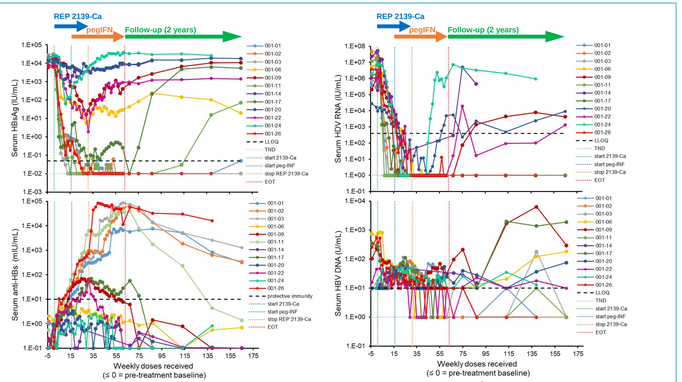

Figure 2. Antiviral response during treatment and follow-up in the REP 301 / REP 301-LTF studies. LLOQ = lower limit of quantification, TND = target not detected, EOT – end of treatment.

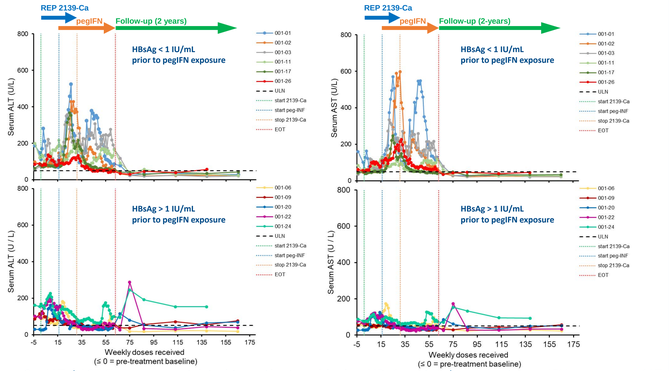

Figure 3. ALT / AST flares are restricted to patients achieving HBsAg < 1IU/mL prior to pegIFN exposure. ALT / AST levels drop below baseline levels or normalize in most patients during follow-up. ULN = upper limit of normal (50 U/L), EOT = end of treatment.

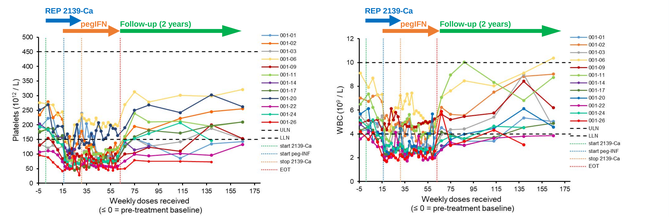

Figure 4. Recovery of platelet and WBC counts to pre-treatment levels was observed in all patients during follow-up.

On treatment: Functional control achieved on treatment (HBsAg < 1IU/mL, HBV DNA < LLOQ)

On treatment: HBsAg reduction > 1 log from baseline but > 1 IU/mL

On treatment: HBsAg reduction < 1 log from baseline

Follow-up: Functional repression of HBV infection (HBV DNA < 1000 IU/mL) when HDV infection is in functional remission

Follow-up: Clinical benefit (normal liver enzymes and declining median hepatic stiffness)

Numbers in bold indicate functional remission of HBV (HBV DNA < LLOQ and normal liver enzymes) or HDV infection (HDV RNA TND) and HBsAg < LLOQ

Numbers in red indicate patients who achieved HDV RNA TND but rebounded in absence of REP 2139-Ca

Patient	Parameter	Baseline	EOT	FW24	F 1Y	F1.5Y	F2Y
001-01	HBsAg (IU/mL)	13988	TND	TND	TND	TND	0.05
	anti-HBs (mIU/mL)	1.03	6633	7585	5073	820	318
	HBV DNA (IU/mL)	< LLOQ	<LLOQ	TND	<LLOQ	TND	TND
	HDV RNA (IU/mL)	394000	TND	TND	TND	TND	TND
	ALT (U/L)	188	80	33	37	27	29
	AST (U/L)	160	111	29	29	25	26
	Med. Hep. Stiffness (kPa)	8.4	17.1	12	10.9	9.3	7.9
001-02	HBsAg (IU/mL)	27264	TND	TND	TND	TND	TND
	anti-HBs (mIU/mL)	1.29	51970	13540	1873	639	345
	HBV DNA (IU/mL)	<LLOQ	TND	inhibition	TND	TND	TND
	HDV RNA (IU/mL)	47100000	TND	TND	TND	TND	TND
	ALT (U/L)	98	53	21	24	25	24
	AST (U/L)	64	61	23	26	24	24
	Med. Hep. Stiffness (kPa)	7.7	9.9	7.3	6.1	5.4	5.7
001-03	HBsAg (IU/mL)	28261	TND	TND	TND	TND	TND
	anti-HBs (mIU/mL)	<0.1	86532	13566	5079	2603	1261
	HBV DNA (IU/mL)	<LLOQ	TND	TND	TND	179	TND
	HDV RNA (IU/mL)	697000	TND	TND	TND	TND	TND
	ALT (U/L)	53	191	20	25	18	21
	AST (U/L)	36	129	24	40	22	23
	Med. Hep. Stiffness (kPa)	14.8	17.1	14.6	12	9.5	9.5
001-06	HBsAg (IU/mL)	17511	29.7	239	146	103	19.6
	anti-HBs (mIU/mL)	2.1	1.13	1.07	0.1	0.56	0.7
	HBV DNA (IU/mL)	726	<LLOQ	13	21	122	183
	HDV RNA (IU/mL)	5490000	TND	TND	TND	TND	TND
	ALT (U/L)	95	53	17	21	21	18
	AST (U/L)	54	57	24	30	28	24
	Med. Hep. Stiffness (kPa)	6.8	7.1	8.1	6.3	4.8	6.7
001-09	HBsAg (IU/mL)	16426	399	2646	6621	10627	10772
	anti-HBs (mIU/mL)	<0.1	7.76	1.42	0.78	<0.1	<0.1
	HBV DNA (IU/mL)	104	31	10	1696	6386	297
	HDV RNA (IU/mL)	211000	TND	1390	4438	7890	4253
	ALT (U/L)	85	34	56	71	54	76
	AST (U/L)	55	29	38	44	42	57
	Med. Hep. Stiffness (kPa)	12	12	10.2	19.8	18.4	14.3
001-11	HBsAg (IU/mL)	12382	<LLOQ	TND	<LLOQ	15.7	71.4
	anti-HBs (mIU/mL)	0.55	34749	1772	231	4.32	1.39
	HBV DNA (IU/mL)	<LLOQ	<LLOQ	TND	TND	<LLOQ	TND
	HDV RNA (IU/mL)	12100000	TND	TND	TND	TND	TND
	ALT (U/L)	200	133	57	29	30	24
	AST (U/L)	85	100	46	27	28	27
	Med. Hep. Stiffness (kPa)	9.6	10.3	6.9	6.6	5.4	7.1
001-17	HBsAg (IU/mL)	8314	0.26	214	4754	6250	5479
	anti-HBs (mIU/mL)	<0.1	28	0.1	0.1	0.11	<0.1
	HBV DNA (IU/mL)	350	<LLOQ	10	1992	1386	1894
	HDV RNA (IU/mL)	1690000	TND	TND	TND	TND	TND
	ALT (U/L)	62	46	29	42	35	43
	AST (U/L)	44	45	30	35	33	34
	Med. Hep. Stiffness (kPa)	9.5	9.8	7.8	8.4	5.1	6.2
001-20	HBsAg (IU/mL)	13430	9964	14943	14917	18955	18162
	anti-HBs (mIU/mL)	<0.1	<0.1	0.19	<0.1	<0.1	<0.1
	HBV DNA (IU/mL)	<LLOQ	25	28	10	37	76
	HDV RNA (IU/mL)	27400	4920	2250	485	2440	9300
	ALT (U/L)	29	47	53	37	64	69
	AST (U/L)	27	50	45	33	50	51
	Med. Hep. Stiffness (kPa)	8.8	10.2	15	9	9.9	9.9
001-22	HBsAg (IU/mL)	7836	917	1225	1281	1508	1386
	anti-HBs (mIU/mL)	<0.1	<0.1	0.3	0.11	0.1	<0.1
	HBV DNA (IU/mL)	16	<LLOQ	23	10	18	<LLOQ
	HDV RNA (IU/mL)	1090000	TND	17	93.8	101	1340
	ALT (U/L)	101	58	33	29	43	38
	AST (U/L)	78	42	28	27	33	33
	Med. Hep. Stiffness (kPa)	11.9	11.8	8.9	11.8	9.4	6.8
001-24	HBsAg (IU/mL)	20473	34201	29724	32519	26814	
	anti-HBs (mIU/mL)	<0.1	<0.1	<0.1	<0.1	<0.82	
	HBV DNA (IU/mL)	<LLOQ	<LLOQ	10	35	13	
	HDV RNA (IU/mL)	1890000	1090000	3280000	2074000	955000	
	ALT (U/L)	160	97	191	153	153	
	AST (U/L)	88	82	133	96	93	
	Med. Hep. Stiffness (kPa)	7.8	8.2	10.4	10.8	9.3	
001-26	HBsAg (IU/mL)	5854	TND	TND	TND	TND	
	anti-HBs (mIU/mL)	0.25	11291	32543	30018	15920	
	HBV DNA (IU/mL)	256	<LLOQ	TND	TND	TND	
	HDV RNA (IU/mL)	3760000	TND	TND	TND	TND	
	ALT (U/L)	85	51	46	39	57	
	AST (U/L)	61	65	48	40	46	
	Med. Hep. Stiffness (kPa)	30.7	27	34.3	33.3	14.6	

Figure 5. Raw response data demonstrating control of HBV and HDV infection and normalization of liver function during the long term follow-up in the REP 301-LTF study. Please refer to legend at top. LLOQ = lower limit of quantification, TND = target not detected

CONCLUSIONS

- REP 2139-Ca uniquely achieves the reduction or loss of HBsAg and HDV RNA in patients with HBV / HDV co-infection.
- Following the suboptimal dosing regimen employed in the REP 301 study:
  - **Functional remission of HDV RNA (TND) persists 1.5-2 years in 7/11 patients.**
  - **Functional remission of HBV infection (HBV DNA < LLOQ) is persistent in 4/11 patients and is accompanied by HBsAg ≤ LLOQ.**
- **An optimized triple combination similar to that used in the ongoing REP 401 study (see Poster FRI-343) promises improved rates of functional remission of HDV and HBV in co-infected patients.**
- Combination therapy with REP 2139-Ca and pegIFN is well tolerated and has not been accompanied by any safety signals 2 years after therapy withdrawal. Including:
  - Reversal and recovery from treatment-induced thrombocytopenia and leucopenia.
  - Normalization of liver function in most patients.
  - Continual reduction or normalization of median hepatic stiffness in most patients.

REFERENCES

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DISCLOSURES

MB and AV are employees and shareholders in Replicor Inc.

CONTACT INFORMATION

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