Updated follow-up analysis in the REP 401 protocol: Treatment of HBeAg negative chronic HBV Infection with REP 2139-Mg or REP 2165-Mg, tenofovir disoproxil fumarate and pegylated interferon alfa-2a

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INTRODUCTION

HBV subviral particles (SVPs) constitute more than 99.99% of circulating HBsAg and act to block immune control of HBV infection. The nucleic acid polymer (NAP) REP 2139 blocks the assembly and release of SVP derived from cccDNA and integrated HBV DNA[1], allowing the efficient clearance of serum HBsAg. This clearance facilitates the restoration of functional control of HBV infection by immunotherapy in HBV and HBV / HDV-co-infection[1,2]. The REP 401 protocol (NCT02565719) is a randomized, controlled trial assessing the safety and efficacy of the lead NAP compound (REP 2139) and a derivative with enhanced tissue clearance (REP 2165) in combination with tenofovir disoproxil fumarate (TDF) and pegylated interferon alfa-2a (peg-IFN) in patients with chronic HBeAg negative HBV infection.

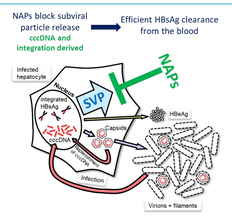

Figure 1. Antiviral mechanism of REP 2139 in HBV infection.

AIMS

- To evaluate the long term safety of combination therapy with REP 2139-Mg or REP 2165-Mg, TDF and pegIFN.
- To evaluate the durability of the functional remission of HBV infection achieved in the REP 401 study.

METHODS

Twenty four weeks of lead-in TDF (300mg PO qD) was followed by randomization (1:1) into experimental and control groups (Table 1). The experimental group received 48 weeks of TDF (300mg PO qD), peg-IFN (180ug SC qW) and REP 2139-Mg or REP 2165-Mg (1:1, 250 mg IV infusion qW) (Table 2). The control group was to receive 48 weeks of TDF + peg-IFN but all patients have crossed over to 48 weeks of experimental therapy in the absence of a 3 log drop in HBsAg after 24 weeks of peg-IFN (see figure below). Viremia is monitored on the Abbott Architect and Realtime platforms.

Table 1. Pre-treatment demographics in the REP 401 study

Parameter		Adaptive comparator control (TDF + peg-IFN)	Experimental (TDF + peg-IFN + NAPs)
Age (average / median)		36.9 / 36	38.6 / 39.5
Sex		27M / 3F	26M / 4F
HBV genotype	A	1	2
	D	19	18
Metavir score (based on Fibroscan)	F0-F1	12	10
	F2	3	6
	F2-F3	0	3
	F3-F4	3	1
Virologic baseline (average / median)	HBV DNA (IU/mL)	$3.6x10^7$ / $8.7x10^4$	$4.8x10^6$ / $4.8x10^4$
	HBsAg (IU/mL	14775.7 / 9302.5	9018.1 / 8743
	Anti-HBs (mIU/mL)	0.78 / 0.1	2.778 / 0.1
ALT (U/L, average / median)		71.65 / 49	91.95 / 56.5

RESULTS

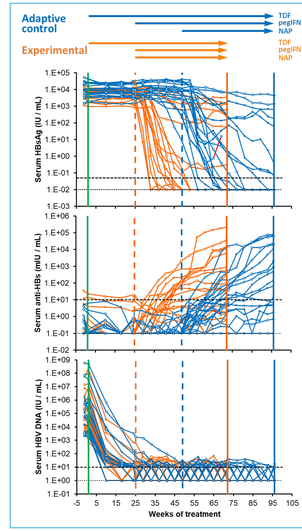

Figure 2. Global antiviral response during treatment in the REP 401 study. *Individual analyses of HBsAg, anti-HBs and HBV DNA during treatment in the adaptive control (blue) and experimental (orange) groups are provided for patients receiving REP 2139 (solid markers) and REP 2165 (hollow markers). Bold dashed horizontal lines indicate the lower limit of quantification (0.05 IU/mL for HBsAg, 10 IU/mL for HBV DNA or 10 mIU/mL for anti-HBs). Fine dashed horizontal lines indicate target not detected (HBsAg and HBV DNA) or no significant anti-HBs present (< 0.1 mIU/mL). The red segment indicates off-treatment rebound in a single REP 2165 adaptive control patient who withdrew from the trial for pegIFN related depression.*

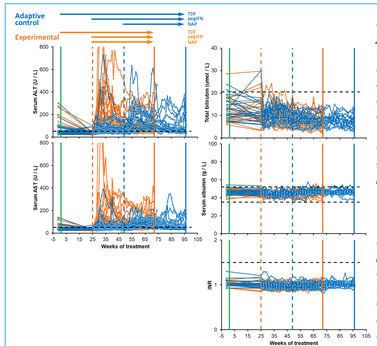

Figure 3. Global liver function during treatment in the REP 401 study. *Individual analyses of ALT/AST (left column) and bilirubin, albumin and INR (right column) during treatment in the adaptive control (blue) and experimental (orange) groups are provided for patients receiving REP 2139 (solid markers) and REP 2165 (hollow markers). Transaminase elevations are restricted to exposure to pegIFN and are substantially more pronounced during NAP-mediated HBsAg clearance. Liver synthetic and secretory function remains normal throughout therapy (right column). Dashed lines indicate upper limit of normal or normal ranges.*

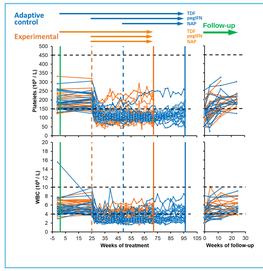

Figure 4. Global recovery of platelet and WBC counts during follow-up in the REP 401 study. *Deflections in platelet counts (top) and WBC counts (bottom) during treatment in the adaptive control (blue) and experimental (orange) groups are provided for patients receiving REP 2139 (solid markers) and REP 2165 (hollow markers). Deflections are correlated with the introduction of pegIFN and are recovering to pre-treatment levels in all patients during follow-up.*

REP 2139-Mg Experimental Group

Patient	GT	Parameter	Baseline	EOT	FW4	FW12	FW24	FW48
01-003	D1	HBsAg (IU/mL)	7809	TND	TND	TND	TND	0.05
		anti-HBs (mIU/mL)	0.61	6147	6287	2631	520	164
		HBV DNA (IU/ mL)	116900	48	10	TND	TND	TND
		ALT (U/L)	32	115	47	33	26	28
		AST (U/L)	28	130	53	35	30	32
02-005	A1	HBsAg (IU/mL)	31184	TND	TND	TND	TND	3.04
		anti-HBs (mIU/mL)	<0.1	920	25419	6551	590	8.45
		HBV DNA (IU/ mL)	2641	30	<LLOQ	<LLOQ	<LLOQ	<LLOQ
		ALT (U/L)	39	304	247	80	45	60
		AST (U/L)	29	292	179	79	45	46
02-015	D1	HBsAg (IU/mL)	10921	3510	4256	4807	4530	4820
		anti-HBs (mIU/mL)	<0.1	0.62	0.14	2.84	4.72	1.35
		HBV DNA (IU/ mL)	43650	15	74	521900	175	1113
		ALT (U/L)	54	50	19	125	19	21
		AST (U/L)	30	68	27	79	27	29
02-024	D1	HBsAg (IU/mL)	1368	TND	TND	TND	TND	TND
		anti-HBs (mIU/mL)	0.64	1.4	1.12	9.14	11	26
		HBV DNA (IU/ mL)	8312	TND	TND	<LLOQ	<LLOQ	TND
		ALT (U/L)	88	58	25	34	23	31
		AST (U/L)	38	39	32	28	28	28
01-046	D2	HBsAg (IU/mL)	8514	TND	TND	TND	<LLOQ	pos*
		anti-HBs (mIU/mL)	0.1	15529	14037	3939	3404	358
		HBV DNA (IU/ mL)	70600000	TND	TND	TND	TND	49*
		ALT (U/L)	112	388	244	37	27	21*
		AST (U/L)	56	315	154	48	37	27*
01-067	D1	HBsAg (IU/mL)	2716	0.31	0.12	0.3	1.91	
		anti-HBs (mIU/mL)	<0.1	4.04	1.58	0.54	0.17	
		HBV DNA (IU/ mL)	194000	TND	TND	14	93	
		ALT (U/L)	55	45	39	34	26	
		AST (U/L)	44	37	29	26	24	
01-026	D1	HBsAg (IU/mL)	8766	TND	TND	TND	TND	
		anti-HBs (mIU/mL)	<0.1	25	26	16	8.01	
		HBV DNA (IU/ mL)	7533000	TND	TND	TND	TND	
		ALT (U/L)	197	124	25	24	21	
		AST (U/L)	117	30	30	31	27	
02-019	D1	HBsAg (IU/mL)	9721	TND	TND	TND	TND	
		anti-HBs (mIU/mL)	<0.1	223055	286756	177925	73157	
		HBV DNA (IU/ mL)	4916	17	1.2	TND	TND	
		ALT (U/L)	41	105	55	36	48	
		AST (U/L)	31	63	37	30	28	
01-077	D2	HBsAg (IU/mL)	1334	TND	TND	TND	TND	
		anti-HBs (mIU/mL)	5.81	38	30	31	28	
		HBV DNA (IU/ mL)	2183000	TND	TND	TND	TND	
		ALT (U/L)	263	70	34	24	19	
		AST (U/L)	78	61	33	25	23	
03-023	D1	HBsAg (IU/mL)	9595	1333	1707	2404		
		anti-HBs (mIU/mL)	12	0.65	0.39	1.58		
		HBV DNA (IU/ mL)	1132000	TND	29	976100		
		ALT (U/L)	175	49	33	91		
		AST (U/L)	85	36	29	63		

REP 2165-Mg Experimental Group

Patient	GT	Parameter	Baseline	EOT	FW4	FW12	FW24	FW48
01-004	D3	HBsAg (IU/mL)	9032	238	240	166		
		anti-HBs (mIU/mL)	<0.1	<0.1	<0.1	<0.1	withdrew consent (recieving NUC therapy)	
		HBV DNA (IU/ mL)	3020	TND	10	26320		
		ALT (U/L)	59	227	138	41		
		AST (U/L)	38	172	82	54		
01-007	D1	HBsAg (IU/mL)	9418	TND	TND	TND	<LLOQ	1.10
		anti-HBs (mIU/mL)	<0.1	331	345	179	44	9.09
		HBV DNA (IU/ mL)	13300	TND	<LLOQ	<LLOQ	TND	TND
		ALT (U/L)	41	82	38	22	17	15
		AST (U/L)	24	62	35	25	19	22
01-010	D2	HBsAg (IU/mL)	14498	1388	1372	1865	5852	
		anti-HBs (mIU/mL)	<0.1	<0.1	<0.1	<0.1	<0.1	Unrelated death
		HBV DNA (IU/ mL)	14190000	10	81	1632000	6320000	
		ALT (U/L)	276	39	20	32	176	
		AST (U/L)	136	47	27	31	70	
01-042	D1	HBsAg (IU/mL)	3049	TND	TND	TND	TND	TND
		anti-HBs (mIU/mL)	<0.1	94	69	20	19	15
		HBV DNA (IU/ mL)	53080	TND	TND	TND	TND	TND
		ALT (U/L)	44	229	90	66	43	39
		AST (U/L)	27	222	72	48	38	32
02-049	D2	HBsAg (IU/mL)	1147	TND	TND	TND	<LLOQ	
		anti-HBs (mIU/mL)	<0.1	547	221	172	87	
		HBV DNA (IU/ mL)	164900	<LLOQ	TND	TND	TND	
		ALT (U/L)	59	28	17	14	19	
		AST (U/L)	55	38	31	26	35	
01-008	D2	HBsAg (IU/mL)	10736	57.9	87.1	1013	1656	
		anti-HBs (mIU/mL)	35	1.5	1.22	1.94	2.67	
		HBV DNA (IU/ mL)	236300	10	15	51910	3009	
		ALT (U/L)	137	54	40	40	23	
		AST (U/L)	74	49	38	44	30	
02-054	D1	HBsAg (IU/mL)	18422	TND	TND	TND	TND	
		anti-HBs (mIU/mL)	<0.1	25	35628	43489	31150	30985
		HBV DNA (IU/ mL)	2130	TND	TND	TND	TND	<LLOQ
		ALT (U/L)	24	62	27	18	18	27
		AST (U/L)	24	61	36	30	27	51
02-058	A2	HBsAg (IU/mL)	8720	TND	TND			TND
		anti-HBs (mIU/mL)	<0.1	13582	16366	Visit missed		7254
		HBV DNA (IU/ mL)	33000	TND	TND			TND
		ALT (U/L)	32	83	45			32
		AST (U/L)	46	77	56			68
01-074	D2	HBsAg (IU/mL)	4835	631	701			
		anti-HBs (mIU/mL)	<0.1	<0.1	<0.1	Visit missed	Visit missed	
		HBV DNA (IU/ mL)	14550	10	80			
		ALT (U/L)	20	73	28			
		AST (U/L)	24	66	34			
03-020	D2	HBsAg (IU/mL)	8577	TND				3.76
		anti-HBs (mIU/mL)	<0.1	148	Visit missed	Visit missed		1.07
		HBV DNA (IU/ mL)	38530	26				76
		ALT (U/L)	51	155				32
		AST (U/L)	41	100				39

*tests performed in the USA (qual HBsAg, quant anti-HBs and HBV DNA using Roche assays)

Patient 03-020 withdrew from treatment early after 24 weeks pf REP 2165+pegIFN+TDF for personal reasons - FW24 was completed upon return.

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)

Follow-up: Clinical benefit (normal liver enzymes)

Follow-up numbers in bold indicate HBV DNA and HBsAg status during functional remission of HBV (HBV DNA < LLOQ)

REP 2139-Mg Comparator Control Group

Patient	GT	Parameter	Baseline	EOT	FW4	FW12	FW24	FW48
01-015	D1	HBsAg (IU/mL)	3648	TND	TND	TND	0.07	
		anti-HBs (mIU/mL)	<0.1	148	257	191	73	
		HBV DNA (IU/ mL)	64100	TND	TND	TND	TND	
		ALT (U/L)	93	55	41	30	25	
		AST (U/L)	38	38	31	29	31	
01-017	D2	HBsAg (IU/mL)	6567	0.39	0.71	3.06	45.9	
		anti-HBs (mIU/mL)	<0.1	15	10	2.46	0.21	
		HBV DNA (IU/ mL)	2404	TND	TND	TND	<LLOQ	
		ALT (U/L)	49	66	41	26	23	
		AST (U/L)	33	53	36	31	29	
01-019	D1	HBsAg (IU/mL)	25957	0.07	0.46	3.31	114	
		anti-HBs (mIU/mL)	<0.1	69	37	8.54	0.17	
		HBV DNA (IU/ mL)	14400	TND	11	<LLOQ	<LLOQ	
		ALT (U/L)	32	65	73	110	82	
		AST (U/L)	29	50	55	79	54	
01-028	D1	HBsAg (IU/mL)	9271	640	1388	2966		
		anti-HBs (mIU/mL)	<0.1	6.47	3.9	1.31		
		HBV DNA (IU/ mL)	779600	11	16	3476		
		ALT (U/L)	38	43	23	21	41	
		AST (U/L)	24	35	23	17	33	
01-023	D2	HBsAg (IU/mL)	10082	184	520	1148	609	
		anti-HBs (mIU/mL)	5.11	1.77	0.94	2.83	1.97	
		HBV DNA (IU/ mL)	1620000	TND	16	48200	102	
		ALT (U/L)	302	40	21	102	37	
		AST (U/L)	139	34	25	60	32	
01-063	D1	HBsAg (IU/mL)	3726	TND	TND	TND		
		anti-HBs (mIU/mL)	<0.1	494	727	865		
		HBV DNA (IU/ mL)	109900	TND	TND	TND		
		ALT (U/L)	81	231	71	21		
		AST (U/L)	40	190	51	23		
02-053	D1	HBsAg (IU/mL)	7101	TND	TND	TND		
		anti-HBs (mIU/mL)	<0.1	84636	71950	57783		
		HBV DNA (IU/ mL)	2151	TND	TND	TND		
		ALT (U/L)	89	69	36	25		
		AST (U/L)	51	45	31	25		
01-075	A2	HBsAg (IU/mL)	32170	64	472	5204		
		anti-HBs (mIU/mL)	<0.1	4.58	3.48	1.54		
		HBV DNA (IU/ mL)	533100	TND	1170	105800		
		ALT (U/L)	39	48	42	34		
		AST (U/L)	28	50	41	37		
01-082	D2	HBsAg (IU/mL)	9334	TND	TND			
		anti-HBs (mIU/mL)	<0.1	11500	26942			
		HBV DNA (IU/ mL)	44900	TND	TND			
		ALT (U/L)	40	45	26			
		AST (U/L)	26	36	27			
02-077	D2	HBsAg (IU/mL)	4897	0.08	0.24			
		anti-HBs (mIU/mL)	<0.1	4.76	3.84			
		HBV DNA (IU/ mL)	2998	<LLOQ	TND			
		ALT (U/L)	42	392	219			
		AST (U/L)	27	192	85			

REP 2165-Mg Comparator Control Group

Patient	GT	Parameter	Baseline	EOT	FW4	FW12	FW24	FW48
02-001	D1	HBsAg (IU / ml)	3375	TND	TND	TND	TND	
		anti-HBs (mIU / ml)	0.68	62184	97729	94362	85258	
		HBV DNA (IU / ml)	505800	TND	TND	TND	TND	
		ALT (U/L)	177	106	38	18	18	
		AST (U/L)	75	65	37	27	28	
02-003	D1	HBsAg (IU/ml)	26824	4476	4491	40528	3681	
		anti-HBs (mIU/mL)	0.2	<0.1	<0.1	0.13	<0.1	
		HBV DNA (IU/ mL)	5820000	TND	2376	7965000	281400	
		ALT (U/L)	87	36	17	185	50	
		AST (U/L)	55	50	28	136	43	
02-010	D2	HBsAg (IU/ml)	18705	15.8	444	6176	14167	26207
		anti-HBs (mIU/mL)	0.47	1.31	<0.1	0.32	<0.1	<0.1
		HBV DNA (IU/ mL)	3850	<LLOQ	10	1268	1162	6949
		ALT (U/L)	22	48	37	45	26	22
		AST (U/L)	22	38	34	36	28	28
02-011	D2	HBsAg (IU/ml)	21232	TND	TND	TND	TND	
		anti-HBs (mIU/mL)	<0.1	19058	22439	13015	900	
		HBV DNA (IU/ mL)	2156	<LLOQ	TND	16	TND	
		ALT (U/L)	31	149	91	69	43	
		AST (U/L)	25	169	100	76	39	
02-018	D1	HBsAg (IU/ml)	23571	1410	2001	3344	4117	
		anti-HBs (mIU/mL)	1.13	0.71	0.69	0.56	20	
		HBV DNA (IU/ mL)	71020000	<LLOQ	3615	4656000	7926	
		ALT (U/L)	51	219	137	56	155	
		AST (U/L)	33	137	86	68	74	
02-036	D1	HBsAg (IU/ml)	53703	TND	TND	TND		
		anti-HBs (mIU/mL)	<0.1	68468	89764	38264		
		HBV DNA (IU/ mL)	5783000000	17	TND	<LLOQ		
		ALT (U/L)	101	52	16	55		
		AST (U/L)	85	66	30	266		
01-069	D2	HBsAg (IU/ml)	4363	TND	TND	TND		
		anti-HBs (mIU/mL)	2.7	1979	592	943		
		HBV DNA (IU/ mL)	440000	TND	TND	TND		
		ALT (U/L)	49	40	17	19		
		AST (U/L)	47	55	30	29		
02-050	D2	HBsAg (IU/ml)	1575	TND	TND	TND		
		anti-HBs (mIU/mL)	4	23069	25426	15308		
		HBV DNA (IU/ mL)	2549	<LLOQ	TND	TND		
		ALT (U/L)	31	41	19	15		
		AST (U/L)	28	49	29	25		
02-057	D1	HBsAg (IU/ml)	7451	TND	TND	TND		
		anti-HBs (mIU/mL)	<0.1	881	783	600		
		HBV DNA (IU/ mL)	189700	TND	TND	TND		
		ALT (U/L)	58	95	34	27		
		AST (U/L)	41	57	31	39		
03-016	D1	HBsAg (IU/ml)	21961	<LLOQ	0.36			
		anti-HBs (mIU/mL)	<0.1	6.97	6.06			
		HBV DNA (IU/ mL)	2827	11	TND			
		ALT (U/L)	21	466	68			
		AST (U/L)	22	202	36			

Patient 02-010 was enterered into follow-up after 16 weeks of REP 2165+pegIFN+TDF due to pegIFN related depression.

Patient 03-016 withdrew from treatment early after 24 weeks pf REP 2165+pegIFN+TDF for personal reasons not related to tolerability.

Figure 5. Global response during treatment and treatment-free follow-up in the REP 401 study. *Raw response data demonstrating functional control of HBV infection during treatment and persistence of functional control of infection during treatment-free follow-up are provided. Qualitative responses during treatment and follow-up are colour-coded according to the legend (bottom left). LLOQ = lower limit of quantification, TND = target not detected*

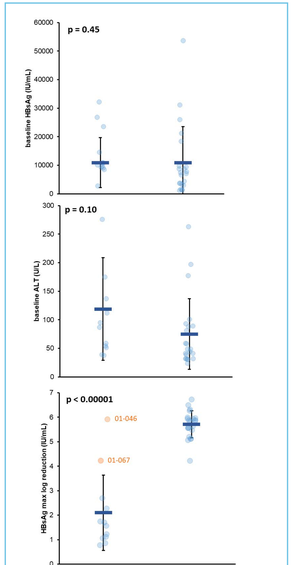

Figure 6. Predicting functional remission of HBV infection in the REP 401 study. *Global analysis of all patients completing therapy and 12 weeks of follow-up are presented. Establishment of functional remission (HBV DNA < LLOQ with ≥ 12 weeks of follow-up) was not predicted by pre-treatment HBsAg (top) or ALT (middle) baselines. Establishment of functional remission was highly correlated to those patients achieving HBsAg reduction ≥ 4 logs from baseline during therapy (bottom). Outlier HBsAg response patients are indicated in orange.*

CONCLUSIONS

- 48 weeks of REP 2139-Mg and REP 2165-Mg used in combination with TDF and pegIFN is safe and well tolerated in patients with HBeAg negative chronic HBV infection and uniquely achieve reduction or loss of HBsAg and HBsAg seroconversion in a high proportion of patients.
- **In patients receiving the lead clinical therapy (upfront combination with REP 2139-Mg, pegIFN and TDF, response rates for achieving functional remission (HBV DNA < LLOQ) and functional repression (HBV DNA < 1000 IU/mL) were 60% and 80% respectively**
- Despite the use of suboptimal regimens where NAPs were added following 24 weeks pf TDF + pegIFN or using the more labile REP 2165-Mg, rates of functional remission and functional repression were still 65% and 75% respectively (in patients completing treatment and 12 weeks of follow-up).
- **Functional remission is highly correlated with HBsAg reduction ≥ 4 log from baseline during therapy**
- **In seven patients, control of HBV DNA (< LLOQ) is currently maintained in the absence of antiviral therapy when anti-HBsAg is < 10 mIU/mL, suggesting the establishment of control of cccDNA in these patients.**
- Introduction of other immunotherapies in place of pegIFN (thymosin alpha 1, TLR agonists or therapeutic vaccines) may further improve response rates.

REFERENCES

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DISCLOSURES

MB and AV are employees and shareholders in Replicor Inc.

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