Establishment of High Rates of Functional Control and Reversal of Fibrosis Following Treatment of HBeAg Negative Chronic HBV Infection with REP 2139-Mg / REP 2165-Mg, Tenofovir Disoproxil Fumarate and Pegylated Interferon Alpha-2a

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INTRODUCTION

Nucleic acid polymers block the assembly and release of HBV subviral particles, allowing clearance of serum HBsAg by host immune function. Previous clinical studies have demonstrated that NAP monotherapy is associated with high rates of HBsAg reduction to < 1 IU/mL and is accompanied by HBeAg and HBsAg seroconversion, HBV DNA, HBV RNA and HBcrAg declines and HDV RNA clearance (in HDV co-infected patients). When used in combination with immunotherapy, control of all of the above are maintained during treatment free follow-up in the majority of patients treated[1].

The REP 401 protocol (NCT02565719) is a randomized, controlled trial assessing the safety and efficacy of REP 2139-Mg and REP 2165-Mg (Table 1) in combination with tenofovir disoproxil fumarate (TDF) and pegylated interferon alpha-2a (pegIFN) in patients with chronic HBeAg negative HBV infection.

MATERIALS AND METHODS

REP 2139-Mg and REP 2165-Mg (magnesium chelate complex) drug products (Table 1) are optimized for subcutaneous (SC) injection but administered via intravenous infusion in the REP 401 study to assess tolerability in preparation for transition to SC in future trials .

Twenty four weeks of lead-in TDF was followed by randomization (1:1) into experimental and control groups. The experimental group received 48 weeks of TDF, pegIFN (180ug SC qW) and REP 2139-Mg or REP 2165-Mg (1:1, 250 mg IV infusion qW). The control group received 24 weeks of TDF + pegIFN with all patients crossing over to 48 weeks of experimental therapy due to poor HBsAg response (see Figure 1). Viremia is monitored on the Abbott Architect and Realtime platforms.

Table 1. REP 2139 vs REP 2165

NAP	Sequence 5' - 3' (A = 2'OMeA or 2'OH A; C = 2'OMe-5-MeC)	Plasma stability 7 days @ 37°C (% of standard)	
		Neutral	Acidified
REP 2139	ACACACACACACACACACACACACACACACACAC	93	86
REP 2165	ACACACACACACACACACACACACACACACACAC	89	36

Replacement of 2'OMe with 2'OH on ribose at adenosines at positions 11, 21 and 31 in REP 2165 results in increased cleavage to 10mer fragments by endonucleases, resulting in accelerated clearance from tissues[2].

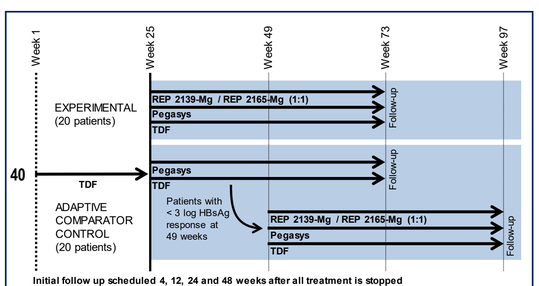

Figure 1. Design of REP 401 study.

Table 2. REP 401 Baseline Characteristics

Parameter		Adaptive comparator control (TDF + pegIFN)	Experimental (TDF + pegIFN + 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	4	7
	F2-F3	0	2
	F3-F4	4	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

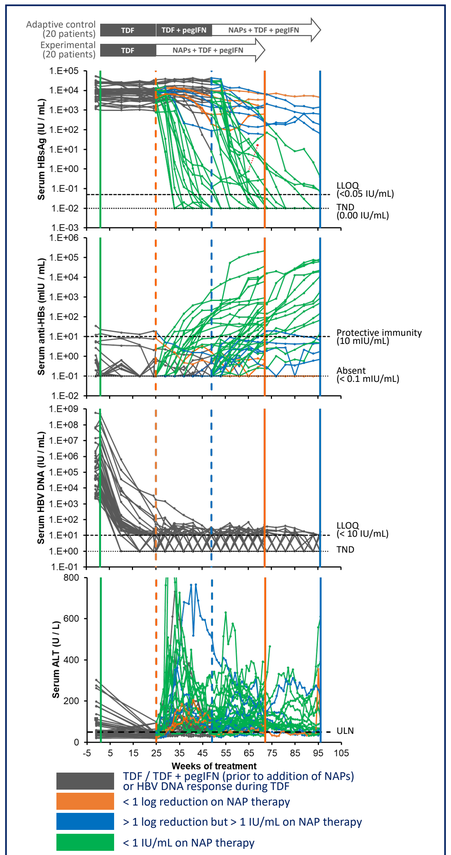

Figure 2. On-treatment responses in the REP 401 study.
Responses to REP 2139-Mg and REP 2165-Mg were indistinguishable. Global individual patient responses are presented for HBsAg, anti-HBs, HBV DNA and ALT and are color-coded according to HBsAg response (see legend above) for HBsAg, anti-HBs and ALT. The red HBsAg segment indicates off-treatment rebound in a single REP 2165 adaptive control patient who entered early into follow-up due to pegIFN related depression.

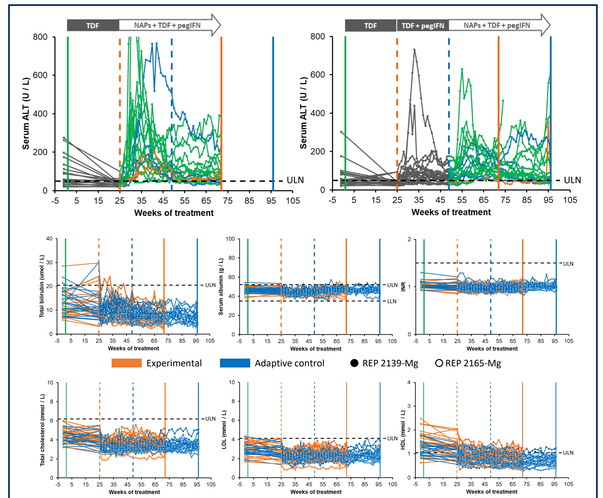

Figure 3. Therapeutic nature of ALT flares in the REP 401 study.
ALT flares with REP 2139-Mg and REP 2165-Mgwere indistinguishable . Individual patient ALT flares in the experimental (top left) and adaptive control (top right) groups are presented and color-coded according to HBsAg response as indicated in Figure 2. ALT flares are self resolving and normalize during follow-up (see Figure 5). ALT flares are generally more prominent amongst strong HBsAg responders but are attenuated in adaptive control patients with where exposure to NAPs occurred after 24 weeks of pegIFN exposure (top right). Globally normal bilirubin, albumin and INR (middle row) and lipid dynamics (bottom row) indicate liver metabolic function was normal during all ALT elevations observed.

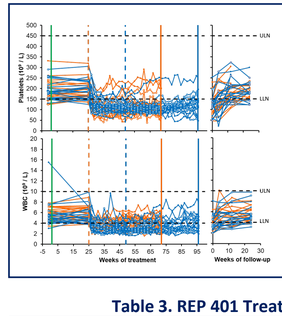

Figure 4. Management of pegIFN induced hematological changes
PegIFN-induced hematological changes were indistinguishable in the presence or absence of NAPs. Global changes in WBC and platelets during treatment and follow-up are provided (see Legend in Figure 3). Mild to moderate changes in WBC and platelets was otherwise asymptomatic and effectively managed with pegIFN dose reduction and / or eltrombopag without affecting antiviral response and recovered to baseline during follow-up.

Table 3. REP 401 Treatment and Follow-up Summary

Patients entered into trial		40
End of treatment HBsAg response	> 1 log from baseline	36 (90%)
	< 1 IU/mL	27 (67%)
	≤ 0.05 IU/mL	24 (60%)
Patients currently completed treatment and 24-48 weeks of follow-up		**34**
Stable, inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		15 (44%)
Functional cure (HBsAg and HBV DNA target not detected)		14 (41%)
Therapy not indicated (AASLD / EASL guidelines) Clinical benefit (Low risk of fibrosis progression and HCC)		**29 (85%)**

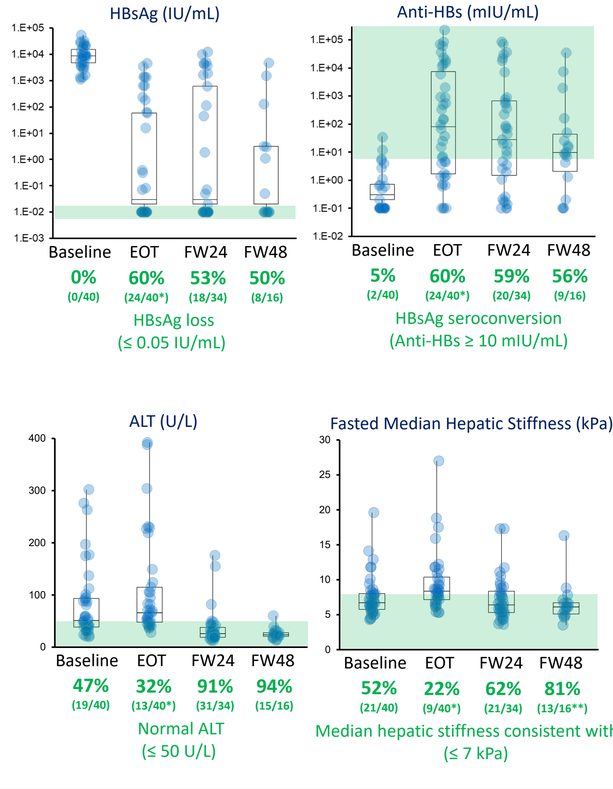

Figure 5. Establishment of high rates of functional control persisting after therapy in the REP 401 study.
Population analysis at baseline, end of treatment (EOT), 24 and 48 weeks of follow-up are presented for HBsAg (top left), anti-HBs (top middle), HBV DNA (top right), serum ALT (bottom left) and fasted median hepatic stiffness (bottom right) are presented. High rates of HBsAg loss, HBsAg seroconversion, undetectable HBV DNA, normal ALT and continual reduction in median hepatic stiffness are chronically persistent after removal of therapy. Summary results are presented in Table 3.

CONCLUSIONS

1. **REP 2139-Mg and REP 2165-Mg are equivalently well tolerated and effective in achieving high rates of HBsAg clearance/loss and seroconversion in a 48 week combination regimen with TDF and pegIFN.**
2. **ALT flares occur in ~ 90% of patients and are likely therapeutic in nature:**
   - **Self resolving**
   - **Otherwise asymptomatic (even in patients with advanced fibrosis)**
   - **Correlated with antiviral responses and establishment of functional control off therapy**
3. **High rates of inactive HBV (44%) and functional cure (41%) are established with accompanying normalization of liver function and apparent reversal of fibrosis.**
4. **85% of patients meet the level of control associated with low risk of progression of liver disease and reduced risk of HCC.**
5. **Although pegIFN is well tolerated, other immunotherapies which do not negatively impact T-cell function[3] may improve upon the functional control achievable when used in combination with REP 2139-Mg.**

DISCLOSURES

MB and AV are employees of and shareholders in Replicor Inc. All other authors have no conflicts to declare.

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