Update on the Safety and Efficacy of REP 2139-Ca Monotherapy and subsequent Combination therapy with Pegylated Interferon Alpha-2A in Caucasian Patients with Chronic HBV / HDV co-Infection

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BACKGROUND

- 15-20 million patients are affected by HBV / HDV co-infection
- Most aggressive form of viral hepatitis with the fastest progression to cirrhosis.
- No approved therapy: Interferon-based treatment can infrequently achieve functional cures with long-term exposure
- HBsAg is a critical component of the HDV life cycle:
  - HBsAg not produced by HDV but is required for its assembly
  - HDV infection only occurs with HBV infection
  - HDV assembly may be linked to the assembly of HBV subviral particles (SVP) (1)
- NAPs have the ability to reduce HBsAg concentration in the serum (2, 3)

➢ **Hypothesis**: Imparing the assembly of SVP may also block HDV virion morphogenesis and/or secretion.

OBJECTIVES

➢ Demonstrate the safety and efficacy of REP 2139 monotherapy and combination with pegylated interferon alpha-2A in HBV/HDV chronic carriers.

MATERIAL & METHODS

• Caucasian patients treated in Chisinau, Moldova
• CRO monitored trial compliant with EU GCP
• Clinicaltrials.org # NCT02233075

12 patients enrolled with HBV / HDV co-infection at the start of treatment:
- Anti-HDAg (+),
- Serum HBsAg > 1000 U / ml
- HBeAg (-),
- Compensated liver disease, mild to moderate fibrosis, non cirrhotic.

Viremia monitored at University of Duisburg-Essen, Germany:
- Abbott PCR (HBV DNA)
- Abbott Architect Quantitative (HBsAg and anti-HBs)
- Robogene RT-PCR (HDV RNA) – validated at two external sites.
- Diasorin (anti-HDAg)
- HDV RNA validated at two external test sites (data not shown).

Dosing in three stages:
1. 15 weeks REP 2139-Ca (calcium chelate complex of REP 2139) 500mg qW IV
2. 15 weeks REP 2139-Ca 250mg qW IV plus pegylated interferon alpha 2a (peg-IFN, 180 ug qW SC)
3. 33 weeks peg-IFN (180 ug qW SC)

➢ 24 weeks of follow-up is planned at the end of peg-IFN therapy

RESULTS

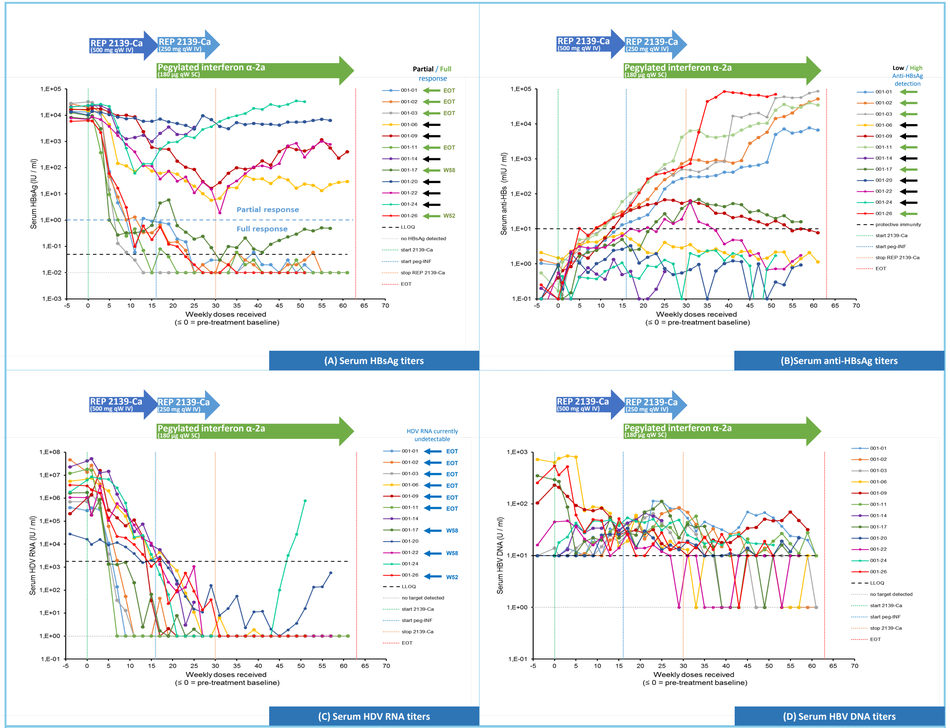


Figure 1. Efficacy of REP 2139-Ca and peg-IFN combined treatment in HBV/HDV coinfected patients. (A) REP 2139-Ca monotherapy results in up to ~ 6 log reductions in serum HBsAg. Full responders are defined by serum HBsAg is < 1 IU / ml prior to peg-IFN addition and partial responders are defined as having serum HBsAg > 1 IU/ml prior to peg-IFN addition. The length of treatment is indicated for each patient ([W]eek). **(B)** Serum anti-HBsAg in treated patients. Substantial anti-HBsAg titers up to >10^4 mIU/ml are observed upon addition of peg-IFN therapy. **(C)** Serum HDV RNA reductions are profound in all patients with 9/12 patients currently having no detectable serum HDV RNA. Importantly, reduction of serum HBsAg was not a prerequisite for the loss of serum HDV RNA, suggesting an additional inhibitory effect of NAPs in HDV lifecycle. **(D)** Serum HBV DNA appears to be partially and transiently de-repressed with reduction in serum HDV RNA in patients 01, 02, 03, 14, 20, 22 and 24. However after de-repression, significant reduction of HBV DNA concentration is observed in many of these patients with the addition of peg-IFN. LLOQ, lower limit of quantification; EOT, end of treatment.

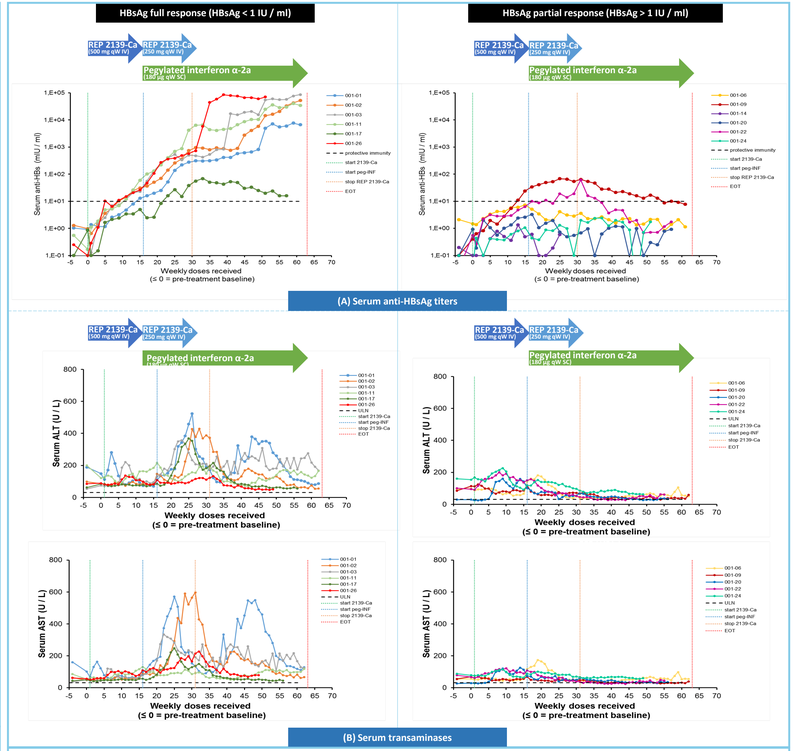
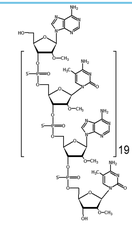


Figure 2. Correlation between serum HBsAg reductions and anti-HBsAg and liver transaminase levels with the start of peg-IFN therapy. (A) Serum anti-HBsAg from full HBsAg responders (left panel) and partial HBsAg responders (right panel) as defined in Figure 1. **(B)** Serum ALT and AST response to treatment. No significant flares are visible with REP 2139-Ca / Pegylated interferon α-2a treatment in partial responders (right panel) and serum transaminase levels appear to normalize as treatment progresses. In the case of full responders (serum HBsAg < 1 IU / ml), significant serum ALT / AST flares are observed upon addition of peg-IFN to the therapy regimen. ULN, upper limit of normal; EOT, end of treatment.

REP 2139 structure



CONCLUSIONS

- ✓ **REP 2139-Ca is able to simultaneously reduce HBsAg and HDV RNA in patients with chronic HBV / HDV co-infection.**
- ✓ **Pharmacologic effect of NAPs on serum HBsAg observed in Asian patients in previous trials is confirmed in Caucasian patients.**
- ✓ **NAPs may have distinct antiviral mechanisms against HBV and HDV lifecycles.**
- ✓ **Increased anti-HBs production and/or liver flares correlated with the start of peg-INF exposure may be related to the extent of clearance of serum HBsAg.**
- ✓ **Longer combination treatment with immunotherapy will likely result in a higher proportion of patients with a full HBsAg response (< 1 IU / ml).**

➢ **NAP-based antiviral therapy may become an important new treatment option for patients with HBV / HDV co-infection.**

REFERENCES

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