SERUM HBV-RNA LEVELS DECLINE SIGNIFICANTLY IN CHRONIC HEPATITIS B PATIENTS DOSED WITH THE NUCLEIC-ACID POLYMER REP 2139-Ca

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Disclosures

• **Hendrik W. Reesink** – *Consulting / Research Support*:
  Abbvie, BMS, Boehringer Ingelheim, Gilead, GSK, Janssen-Cilag, Merck/MSD, PRA-International, Regulus, Replicor, Roche, R-Pharm, Santaris.

• **Andrew Vaillant, Michel Bazinet** – *Stockholders (shareholder) and Employees*:
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• **The following people have nothing to disclose:**
  Louis Jansen, Femke Stelma, Karel van Dort, Neeltje Kootstra, Mamun Al-Mahtab.
Available therapies for patients with chronic hepatitis B:\(^1\):

- **Peginterferon-\(\alpha\)**
  - Potential immune-mediated control of HBV
  - Significant side-effects

- **Nucleos(t)ide analogues**
  - Potent viral suppression
  - Limited off-therapy response

Need for new therapeutic approaches:

⇒ Enhance loss of HBeAg and HBsAg

1. EASL. *J Hepatol* 2012.
Hypothesis

Serum Hepatitis B RNA levels in NUC treatment?

Nucleic Acid Polymers (NAPs) in Hepatitis B

• NAPs have entry and post entry antiviral effects in HBV infection in vitro\textsuperscript{1}
• The post-entry NAP effect appears to be linked to clearance of serum HBsAg\textsuperscript{2}

Hypothesis:
• NAPs prevent subviral particle (SVP) formation

REP 2139 = (A,5’MeC)\textsubscript{20} PS-ON, fully 2’O-methylated

REP 2139-Ca = Calcium chelate complex of REP 2139 (improves administration tolerability)

Hypothesis

*Serum Hepatitis B RNA levels in NAP treatment?*

**Elimination of serum HBsAg**

**Restoration of immune response?**

**Serum HBV RNA?**

Research Question

- Kinetics of serum HBV-RNA in patients dosed with nucleic acid polymer (NAP) REP 2139-Ca?

**REP 102** protocol: Phase II proof of concept trial
Dr. Mamun Al-Mahtab, (Dhaka, Bangladesh)
Dosing: 2011 – 2012, Follow-up *ongoing*
Patient Cohort

Inclusion criteria REP 102 protocol

- 12 Chronic Hepatitis B patients
- HBeAg-positive
- HBV DNA $10^5 - 10^8$ copies / mL
- Treatment naive
- Metavir $\leq$ F3 (fibroscan)
- ALT $< 3 \times$ ULN
Patient Cohort

Study dosing REP 102 protocol

$\begin{align*}
\text{n = 12} & \quad \text{REP 2139-Ca} \\
\text{20-24 Weeks} & \\
\text{REP 2139-Ca} & \text{– 500mg qW 2 hour IV} \\
\text{*Add-on:} & \quad \text{Pegasys™ 180 ug SC qW} \\
& \quad \text{and/or} \\
& \quad \text{Zadaxin™ (thymosin alpha-1) 1.6mg SC 2qW}
\end{align*}$

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Patient Cohort

Time points of HBV RNA measurement

- Serum (-20°C) sent to AMC for HBV RNA measurement
- Compared to HBV DNA (Cobas), and HBsAg (Architect)
Methods

**Serum HBV RNA Quantification**

- RNA isolation in plasma
- DNAse treatment
- Quantitative RT-PCR specific for HBV-RNA

Results

Baseline Serum HBV RNA Levels

Baseline

HBV DNA
\( r^2 0.74, \ p < 0.001 \)

HBsAg
\( r^2 0.33, \ p = 0.049 \)
Results

**Serum HBV-RNA Decline During REP 2139-Ca Treatment**

Week 20-24 Decline

- **NR**
  - $n = 3$

- **R**
  - $n = 9$

Week 20-24 Decline

HBV RNA (log$_{10}$C/mL) vs. Weeks of REP 2139-Ca

Decline from baseline

RNA

HBsAg

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Results

Serum HBV-RNA in REP 2139-Ca Responders (n = 9)

Mean ± SEM
HBV DNA, HBV RNA; log_{10} C/mL
HBsAg; log_{10} IU/mL
anti-HBs; U/L

At FU: 4/9 patients
HBsAg <0.05 IU/mL
+ anti-HBs positive
Results

Serum HBV-RNA in REP 2139-Ca Non-Responders (n = 3)

Mean ± SEM
HBV DNA, HBV RNA; log₁₀ C/mL
HBsAg; log₁₀ IU/mL
anti-HBs; U/L

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Conclusions

• Treatment of CHB patients with REP 2139-Ca resulted in a pronounced decline of serum HBV-RNA in 9/12 of patients.

• In 3/12 patients (non-responders) HBV-RNA levels were unaffected, both before and after treatment with entecavir.

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